UNITED STATES DISTRICT COURT
SOUTHERN DISTRICT OF NEW YORK

IN RE PFIZER INC. SECURITIES LITIGATION	No. 04-cv-9866 (LTS) (DFE)

PFIZER DEFENDANTS' MEMORANDUM OF LAW IN SUPPORT OF THEIR MOTION TO EXCLUDE CERTAIN PLAINTIFFS' EXPERTS' OPINIONS REGARDING CELEBREX AND BEXTRA

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PRELIMINARY STATEMENT

Defendants submit this memorandum of law in support of their motion, pursuant to Federal Rule of Evidence 702, to exclude the following testimony offered by Plaintiffs' experts: that prior to December 16, 2004, there existed reliable scientific evidence that Celebrex and/or Bextra was associated with a statistically significant increase in the risk of thrombotic cardiovascular events such as heart attacks and strokes.

In April 2005, following the removal of Vioxx from the market, the U.S. Food and Drug Administration ("FDA") recommended that all anti-inflammatory medications, including older anti-inflammatories like prescription Motrin (ibuprofen) and Aleve (naproxen), include new labeling that warns of the potential risk of heart attacks and strokes. For Celebrex, the recommendation was based on a trial known as "APC," the results of which were first available to Pfizer on December 16, 2004 and which Pfizer publicly announced the very next day.

APC was one of several experimental studies by U.S. government researchers to see whether very high doses of Celebrex (two and four times the dose most commonly prescribed to patients in the community) taken daily for years could help prevent various types of cancer. While the study showed that Celebrex has promise as a cancer fighting medication, it also showed that Celebrex patients experienced statistically more heart attacks and strokes than patients taking sugar pills. APC was the first and only trial out of hundreds of Celebrex trials to show a statistically significant difference in the occurrence of heart attacks and strokes. Moreover, no Celebrex clinical trial since APC has replicated the results seen there, including other high-dose, long-term trials involving patients at high risk for cardiovascular disease. Celebrex remains on the market today and is a widely prescribed medication because it helps millions of people lead better lives.

Bextra, Pfizer's other anti-inflammatory medication, no longer remains on the market because patients taking Bextra had an increased risk of severe skin reactions compared to patients taking other anti-inflammatory medications. Before withdrawal of the medication, no

clinical trial ever showed that approved uses of Bextra increase the risk of heart attacks and strokes. One experimental open heart bypass surgery study in which patients took very high doses of Bextra in combination with very high doses of an unapproved, intravenous anti-inflammatory compound known as parecoxib showed an increased risk of certain cardiovascular conditions. That same study, however, showed no reliable, statistically significant evidence that even high doses of Bextra in the absence of experimental, intravenous parecoxib increase the risk of the same cardiovascular conditions.

Against this backdrop, Plaintiffs have designated six experts to opine that there existed reliable scientific evidence that Celebrex and/or Bextra was associated with a statistically significant increase in the risk of thrombotic cardiovascular events such as heart attacks and stroke prior to December 16, 2004. In order for that testimony to be admissible under Rule 702 and the Supreme Court's decision in *Daubert v. Merrell Dow Pharmaceuticals, Inc.*, 509 U.S. 579 (1993), and its progeny, Plaintiffs must show that: (i) their proposed experts have the necessary qualifications in their claimed fields of expertise; (ii) their proposed testimony will assist the trier of fact; and (iii) the experts' opinions rest on a reliable methodology (*i.e.*, one that is valid and applicable to the facts in question). This Court has recognized that Rule 702 establishes a "gatekeeper" function, requiring "that the trial court make a 'preliminary assessment of whether the reasoning or methodology underlying the testimony is scientifically valid and of whether that reasoning or methodology properly can be applied to the facts in issue.'" *Montefiore Med. Ctr. v. American Prot. Ins. Co.*, No. 00Civ.3235LTSMHD, 2003 WL 21108232, at *2 (S.D.N.Y. May 13, 2003) (Swain, J.) (*quoting Daubert*, 509 U.S. at 592-93).

As discussed below, the "expert" opinions which Plaintiffs seek to offer here suffer from many of the same methodological flaws that led Judge Charles R. Breyer to exercise his "gatekeeper" function under Rule 702 in related product liability litigation. *See In re Bextra & Celebrex Mktg. Sales Pracs. & Prod. Liab. Litig.*, 524 F. Supp. 2d 1166, 1181 (N.D. Cal. 2007) (precluding plaintiffs from introducing expert evidence that patients taking Celebrex at doses of 200 milligrams ("mg") daily were at an increased risk of thrombotic events compared to patients

taking no medication). In excluding such evidence, Judge Breyer found that the methodology of certain plaintiffs' experts was invalid because they first reached a conclusion and then cherry-picked data to support that conclusion, while rejecting or ignoring the evidence that contradicted their opinions. *See id.* at 1176, 1181. As a result, Judge Breyer held that the "analytical gap" between the data and the experts' conclusions was "simply too great to make the opinion admissible." *Id.* at 1181 (*citing GE Co. v. Joiner*, 522 U.S. 136, 146 (1997)); *see also In re Rezulin Prods. Liab. Litig.*, 369 F. Supp. 2d 398, 437 (S.D.N.Y. 2005) (noting that "courts have excluded expert testimony 'where the expert selectively chose his support from the scientific landscape'") (citation omitted).

Here, the Plaintiffs' experts resort to the same unreliable methodologies. To support some opinions, they employ no methodology. In other instances, they contrive methodologies for the courtroom, which conflict with the methodologies even they use outside the courtroom. And, in other instances, they invent new methodologies that have no precedent or support in the medical and scientific communities.

For example, to support their Celebrex opinions, Plaintiffs' experts reviewed the Celebrex clinical trial results, and then fabricated new methodologies that were intended to contrive "statistically significant" differences in the occurrence of certain combinations of adverse events. However, the "statistically significant" differences are merely the products of their unreliable methods, and such differences would not exist if these experts used valid methodologies and standards. These methodologies are unreliable for many reasons, including because Plaintiffs' experts: (1) use new definitions ("composite endpoints") of cardiovascular safety, which never have been used by doctors and scientists to evaluate the risk of heart attacks, strokes, or any other recognized cardiovascular condition – including by FDA in evaluating these very same studies; (2) improperly manipulate their adverse event counts to skew the data against Celebrex; and (3) arbitrarily change the classification of certain patients' medical conditions in the trials, again improperly biasing the adverse event counts against Celebrex.

Similarly, while Plaintiffs' experts concede that no Bextra clinical trial demonstrates a reliable, statistically significant increase in the risk of heart attack and stroke, they assume that experimental open heart bypass surgery trials involving high doses of unapproved, intravenous parecoxib can be used to support their Bextra opinions. However, these experts proffer no accepted methodology to support this assumption, no analysis that compares and contrasts the cardiovascular effects of the two medications, and no explanation of the undisputed differences in those effects. Moreover, even if Plaintiffs' experts' parecoxib assumptions could be supported with valid methods – which they cannot – the experimental parecoxib trials still do not show reliable, statistically significant differences in the occurrence of heart attacks and strokes.

Thus, the methodologies used by Plaintiffs' experts simply do not satisfy the *Daubert* requirement that experts "employ[] in the courtroom the same level of intellectual rigor that characterizes the practice of an expert in the relevant field." *Kumho Tire Co. v. Carmichael*, 526 U.S. 137, 152 (1999). Accordingly, the Court should preclude each of Plaintiffs' experts from offering the opinion that prior to December 16, 2004, there existed reliable scientific evidence that Celebrex and/or Bextra was associated with a statistically significant increase in the risk of heart attacks and strokes, for several reasons:

David Madigan. Madigan, one of Plaintiffs' three statisticians with no medical training, combined data from certain Celebrex clinical trials and attempted to conduct what is known as a "meta-analysis." In order to conduct his meta-analysis, Madigan required the assistance of medical doctors who, unlike him, are qualified to define an acceptable composite endpoint to measure the risk of medical conditions such as heart attack and stroke. However, rather than consulting with a cardiologist or using an endpoint that is generally accepted by the cardiology community – including those used by FDA in its analysis in April 2005 and by Madigan himself as an expert witness in the Vioxx litigation – Madigan instead made up a new composite endpoint measure never before used by clinical researchers studying the effects of Celebrex or any other anti-inflammatory medication. He also collected data from the Celebrex clinical trials in a haphazard, undocumented way and missed documented adverse events, which should have

been included according to his own composite endpoint and which would have changed his results if he had included them.

To compound these problems, Madigan initially relied on another of Plaintiffs' experts – Lawrence Baruch, who never has classified events in the context of clinical research – to decide how to classify the cardiovascular events that Madigan did not miss. Baruch, the only cardiologist proffered by Plaintiffs, acknowledged that he was not familiar with the composite endpoint measures chosen by Madigan and could not recall ever using those measures himself or even reading a published paper that used them. Moreover, Baruch only had a spreadsheet given to him by Plaintiffs' counsel containing one-line descriptions of patients' medical information from which to make the complex medical judgments required, not the original source of the patients' medical information and other data necessary for such judgments. Baruch could not remember (and did not document) what criteria he used to classify the events, he could not authenticate the spreadsheet Plaintiffs' counsel say reflects the results of his classification, and he admitted that he therefore could offer no objective proof that he had applied the correct criteria or that his classifications were correct. In fact, Baruch was careful to distinguish his efforts from the formal processes employed in clinical research. Even with Baruch's post hoc, unwritten, unprecedented, and informal methodology, Madigan's initial results did not show a statistically significant difference in the occurrence of events that fit Madigan's new definition of cardiovascular safety.

Apparently dissatisfied with Madigan's first effort, Plaintiffs' counsel asked another one of Plaintiffs' experts – Curt Furberg, an administrator at Wake Forest University who is not a cardiologist, has not treated patients in more than thirty-five years, cannot define a heart attack without reference materials, and has not classified events formally in the context of clinical research in more than thirty years – to *reclassify* certain cardiovascular outcomes found by Madigan. Like Baruch, Furberg did not review the available patient medical records; he likewise relied solely on the single-line descriptions in a spreadsheet. Also, like Baruch, Furberg could not remember and did not document the criteria he used to classify the events, he could not

authenticate the spreadsheet Plaintiffs' counsel said reflected the results of his reclassification, and he admitted that his reclassification process was an unprecedented departure from the formal process he and others use in clinical research outside of litigation. Unlike Baruch, however, Furberg classified more of the medical conditions of interest as having occurred in patients taking Celebrex, enabling Madigan to change his results and to contrive a statistically significant difference in the occurrence of medical conditions that fit his unprecedented endpoint measures of cardiovascular safety. Madigan's Celebrex analysis – including Baruch's classification and Furberg's reclassification – is no different than changing or refusing to count certain votes after an election – without an objective and reliable process for doing so. Such practices also are a far cry from the level of intellectual rigor that characterizes the accepted practices of experts in the clinical research field, and the Court should exclude it.

Curt D. Furberg. Furberg never has been licensed to practice medicine in the U.S., has not prescribed a medication in more than thirty-five years, and admits that he is not competent to practice medicine today. In addition to his participation in Madigan's flawed analysis, Furberg also purports to opine on the cardiovascular safety of Celebrex and Bextra based on a small number of cherry-picked clinical trials that he claims support his view that Celebrex and Bextra are unsafe. Furberg does not employ – as he must – a reliable and consistent endpoint definition to measure cardiovascular safety from trial to trial; instead, he varies his safety definition depending on the results of each trial.

For example, even according to the Plaintiffs' experts, a high-dose, experimental trial in 425 patients intended to evaluate whether Celebrex could attenuate the tragic progression of Alzheimer's disease (known as the "Alzheimer's 001" trial) is the only Celebrex clinical trial that preceded APC in December 2004 that allegedly showed a statistically reliable increase in cardiovascular risk. Furberg does not evaluate the Alzheimer's 001 trial based on the number of heart attacks and strokes, however; instead, Furberg contrives a new, unprecedented definition of adverse events never before used in a clinical trial or the peer-reviewed literature. Furberg engages in this results-oriented, post hoc review of the data even though he routinely criticizes

such practices outside of litigation. Furberg's creation of new endpoint definitions to measure cardiovascular safety is no different than creating new voting district boundaries in order to change the winner of an election – after the votes are in and one already knows the distribution of votes by precinct.

Furberg's Bextra analysis is similarly unreliable. He admits that there is no statistically reliable evidence of an increased risk of heart attacks and strokes for patients taking approved doses of oral Bextra pills for arthritis, but he nonetheless jumps from clinical trial to clinical trial to try to divine "signals" and "trends" that he thinks might suggest risk, notwithstanding that he admits there are no objective standards or criteria to evaluate the reliability of his "signal" and "trend" methodologies. Furberg also assumes that the cardiovascular effects of experimental intravenous parecoxib are the same as those of oral Bextra pills, even though he offers no reliable basis or methodology for doing so. Indeed, outside of litigation, he himself has written that intravenous forms of medications differ from oral forms, but here he did not even examine the different cardiovascular effects of the medications. In any event, he is not qualified to evaluate the physiological differences between open heart bypass surgery patients taking high doses of experimental, intravenous parecoxib and outpatients taking Bextra pills for arthritis. Even if Furberg's assumption is valid – and it is not – he has conceded outside of litigation that even the parecoxib trials involving open heart bypass surgery patients did not show statistically reliable evidence of an increased heart attack and stroke risk.

Richard A. Kronmal. Kronmal, another one of Plaintiffs' three statisticians, also admits that in preparing his expert opinions, he used a methodology that departs from methodologies he employs outside of litigation. He conceded that his assignment was not to assess the existing data to determine whether Celebrex or Bextra were associated with thrombotic risk; instead, he was asked to *assume* such an association and find any evidence in support of that assumption. Like Madigan and Furberg, Kronmal chose his own endpoint definitions of cardiovascular safety *after* knowing the results of the clinical trials and despite having no medical training in the biology, diagnosis, and treatment of the medical conditions included in his definitions. Even

with his flawed methodology, Kronmal admits that APC was the first trial to demonstrate statistically reliable evidence that Celebrex increases the risk of heart attacks and strokes – a conclusion with which Judge Breyer agreed. *See In re Bextra*, 524 F. Supp. 2d at 1181-82 (noting that APC is the only evidence of increased risk at 400 mg daily and that there is no reliable evidence of an increased risk at 200 mg daily, the most prescribed dose).

Lawrence Baruch. Baruch is a rebuttal expert and the only cardiologist among Plaintiffs' six experts. In addition to his role in Madigan's Celebrex classification, Baruch offers opinions relating primarily to the experimental parecoxib trials that involved patients who underwent open heart bypass surgery. Like Furberg, Baruch admits that there is no statistically reliable evidence of an increased risk of heart attacks and strokes for patients taking approved doses of oral Bextra. However, also like Furberg, Baruch asserts that parecoxib and Bextra have the same effects, even though he offers no reliable methodology to evaluate the effects of the two medications and he is not qualified to evaluate the significant physiological differences between open heart bypass surgery patients taking high doses of intravenous parecoxib and outpatients taking oral Bextra pills for arthritis.

Joel S. Bennett. Dr. Bennett is plaintiffs' mechanism expert. Bennett's report focuses on the "imbalance" hypothesis, which posits that selective COX-2 inhibitors like Celebrex and Bextra tip the balance of certain substances in the body in a way that makes blood more likely to clot, thereby increasing the risk of clotting events like heart attack and stroke. Both inside and outside the courtroom, however, Bennett has admitted that his theory is speculative and is not testable in humans. Bennett also concedes that, before the APC results become available, there was no reliable, statistically significant evidence that Celebrex increases the risk of heart attacks and strokes. With respect to the experimental parecoxib trials, he also concedes that patients undergoing open heart bypass surgery are in a much different physiological state than outpatients who take Bextra pills for arthritis.

Nicholas P. Jewell. Finally, Plaintiffs retained Jewell, their third statistician, as a rebuttal expert to critique the opinions offered by Pfizer's expert biostatistician, Dr. L.J. Wei. One of

Jewell's criticisms is that Wei should have used a certain statistical test that would make Celebrex look less safe for the heart, even though Plaintiffs' own expert Furberg refers to such a test as "cheating." When Plaintiffs moved to exclude Wei's opinions based on Jewell's claims in the Celebrex product liability litigation, Judge Breyer rejected all of Jewell's criticisms and denied Plaintiffs' motion. *See In re Bextra*, 524 F. Supp. 2d at 1184.

Expert opinions must reflect sound science, and courtroom methodologies must be as intellectually rigorous as those used by clinical researchers who research and develop medications outside the courtroom. Plaintiffs' experts' methodologies here are not. Thus, the Court should exclude any expert opinion that the Celebrex or Bextra data showed reliable evidence of an increased heart attack or stroke risk before December 16, 2004.

STATEMENT OF FACTS

The following sections describe the undisputed methods for evaluating clinical research results using appropriate methodologies (Section I) and what the Celebrex and Bextra data show when that data is analyzed using those undisputed methodologies (Section II).

I. UNDISPUTED METHODS TO EVALUATE CLINICAL RESEARCH RESULTS

The following methodological principles are used by the medical and scientific community to design and evaluate the results of clinical trials, as well as other data. As demonstrated below, these principles are undisputed by some or all of Plaintiffs' experts.

A. Randomized Clinical Trials And Observational Studies

To determine whether a medication increases the risk of a certain disease or an adverse health outcome, researchers conduct two types of studies: (1) randomized clinical trials, and (2) observational studies. In a randomized clinical trial, the subjects are "randomly assigned to one of two groups: one group exposed to the agent of interest and the other not exposed. After a period of time, the study participants in both groups would be evaluated for development of the disease." Fed. Jud. Ctr., *Ref. Man. on Sci. Evid.* 338 (2d ed. 2000) (hereinafter "*Ref. Man.*"), *available at* http://www.fjc.gov/library/fjc_catalog.nsf (last visited July 16, 2009); *see also*

Declaration of Gregory A. Markel, dated July 17, 2009 (the "Markel Declaration" or "Markel Decl."), Ex. 1 at 14 (Furberg Rep.), Markel Decl., Ex. 2 at 4 (Kronmal Rep.). Assigning patients randomly to one group or the other "minimizes the likelihood that there are differences in relevant characteristics between those exposed to the agent and those not exposed." *Ref. Man.* at 338. Randomized trials are "considered the gold standard for determining the relationship of an agent to a disease or health outcome" and are "the best way to ensure that any observed difference between the two groups in outcome is likely to be the result of exposure" to the medication rather than unrelated factors. *Id.*; *see also* Markel Decl., Ex. 1 at 14 (Furberg Rep.); Markel Decl., Ex. 2 at 4 (Kronmal Rep.).

A researcher performing an observational study, by contrast, does not randomize patients into treatment groups. Instead, the researcher observes individuals who have been exposed to the medication and compares them with individuals who have not. *See Ref. Man.* at 339. Because the researcher cannot control for risk factors or other demographic characteristics through randomization, "the investigator addresses their possible role in the relationship being studied by considering them in the design of the study and in the analysis and interpretation of the study results." *Id.*; *see id.* at 93-94, 342, 354-55. Compared to clinical trials, observational studies are more likely to include patients who take the medication at the doses used in the community. *See id.* at 339; Markel Decl., Ex. 3 at 190-97 (Bennett Dep., *In re Bextra*). Moreover, observational studies typically analyze very large numbers of patients, thereby reducing the play of chance. *See Ref. Man.* at 125-26, 357; Markel Decl., Ex. 3 at 72-73 (Bennett Dep., *In re Bextra*).

B. Post Hoc Analyses Of Clinical Trial Results

Clinical trials are prospectively designed, with precise rules spelled out in a written protocol before the trial commences. The protocol identifies the medical question the study is designed to answer, what adverse events should be counted (and how) in order to answer that medical question, and what statistical tests will be applied to help evaluate whether observed differences in the medical outcomes of interest are due to the play of chance. *See* Markel Decl.,

Ex. 4 at 10-11, 16 (Lawrence M. Friedman, Curt D. Furberg, and David L. DeMets, FUNDAMENTALS OF CLINICAL TRIALS, 2 (3d ed. 1998) ["FUNDAMENTALS OF CLINICAL TRIALS"]). By spelling out the rules in advance, there is less opportunity for a researcher to manipulate them after the fact in order to create differences that fit a desired result. *See* Markel Decl., Ex. 5 at 11-12, 39 (Bengt D. Furberg & Curt D. Furberg, EVALUATING CLINICAL RESEARCH: ALL THAT GLITTERS IS NOT GOLD, 11-12 (2d. ed. 2007) ["EVALUATING CLINICAL RESEARCH"]).

By contrast, a post hoc analysis is one that retrospectively evaluates potential effects of a medication that the clinical trial was not designed in advance to study. *See* Markel Decl., Ex. 5 at 141 (EVALUATING CLINICAL RESEARCH). Data may be analyzed on a post hoc basis either by a trial-by-trial analysis, which various of Plaintiffs' experts refer to as an "overview," s*ee* Markel Decl., Ex. 4 at 308-10 (FUNDAMENTALS OF CLINICAL TRIALS), or by a meta-analysis, which is a quantitative technique that combines the results of multiple clinical trials. *Ref. Man.* at 380. In either an overview or a meta-analysis, if a researcher already knows the results of clinical trials, it is possible to construct rules that create the appearance of an association by: (1) picking what to measure (and how to measure it) based on knowledge of the results, (2) changing the statistical tests based on knowledge of the results, or (3) running numerous statistical tests to find one that leads to the hoped-for outcome.[1] As a result, post hoc analyses are used primarily to generate hypotheses for further study, and the medical and scientific community—including Plaintiffs' experts—view them quite skeptically.[2]

[1] *See* Markel Decl., Ex 4 at 311-12 (FUNDAMENTALS OF CLINICAL TRIALS ["[U]nless the goals of the meta-analysis are clearly stated a priori, a positive result can be found in this analysis by undertaking numerous attempts."]); Markel Decl., Ex. 6 at 70-71 (Furberg Dep., *Valenzuela v. Warner-Lambert Co.*); Markel Decl., Ex. 8 at 75 (Furberg Dep.).

[2] *See* Markel Decl., Ex. 5 at 123 (EVALUATING CLINICAL RESEARCH ["Post hoc analyses of data derived from clinical trials designed to answer other research questions are perhaps the least reliable."]); Markel Decl., Ex. 4 at 132 (FUNDAMENTALS OF CLINICAL TRIALS); Markel Decl., Ex. 8 at 92-93 (Furberg Dep.).

C. Accepted Methods Of Conducting Clinical Trials And Post Hoc Analyses

Whether a researcher is designing a clinical trial, an observational study, or a post hoc analysis (via an overview or a meta-analysis), there are certain generally accepted principles that must be followed to ensure that the results are reliable and free from bias. For example, a researcher should: (1) specify in advance a valid clinical question, which is accepted by medical doctors who specialize in the medical condition in question; (2) systematically apply an "endpoint" or measure of the medical condition in question, which is accepted by medical doctors specializing in that medical condition; (3) reliably collect and classify the endpoint events or medical outcomes in a manner that follows accepted criteria for diagnosing those outcomes; and (4) use statistics to evaluate the probability that observed differences between the groups, if any, are due to the play of chance.

1. Specify a Clinically Valid Research Question in Advance

Prior to conducting a clinical trial, an investigator must pre-specify a research hypothesis that is valid according to medical doctors who specialize in the condition of interest. *See* Markel Decl., Ex. 5 at 11-12, 42 (EVALUATING CLINICAL RESEARCH); Markel Decl., Ex. 8 at 85-86 (Furberg Dep.); *id.* at 92-93. Plaintiffs' expert Furberg has written: "A randomized clinical trial is like a horse race that tests the generated hypothesis. Hypotheses (bets) must be 'placed' prior to performing the trial (running the race)." Markel Decl., Ex. 5 at 39 (EVALUATING CLINICAL RESEARCH). Stating the research question in advance "provide[s] protection against post hoc 'hypotheses' that are formulated to fit the observed results." *Id.* at 11-12. Post hoc hypotheses developed after the results are in are a way to "cheat" by betting on the winning horse after the race is run. *Id.* at 40. The question should be framed in a neutral and unbiased way, and, once selected, the question cannot be changed to fit the data. Markel Decl., Ex. 112 at 8 (Furberg Expert Witness Declaration, Baycol Litigation); Markel Decl., Ex. 5 at 11-12 (EVALUATING CLINICAL RESEARCH). "As in a clinical trial protocol, the questions and the criteria [of a post hoc analysis] should be stated in advance." Markel Decl., Ex. 4 at 311 (FUNDAMENTALS OF CLINICAL TRIALS); *see also* Markel Decl., Ex. 10 at 298 (Furberg & Morgan, STAT. MED.

1987;6:295-303 ["The same detail required for clinical trial protocols should be applied to protocols governing the conduct of overviews."]).

2. Systematically Apply a Clinically Valid Endpoint

When a clinical trial investigator specifies the research question in advance, a physician with expertise in the medical condition of interest must specify the medical outcome of interest such as heart attacks (known as an endpoint), or a set of events or outcomes of interest, such as heart attacks, strokes, and sudden deaths that are linked biologically or clinically by a common underlying disease mechanism (referred to as a composite endpoint). Markel Decl., Ex. 5 at 90 (EVALUATING CLINICAL RESEARCH ["The components of the composite endpoint should make clinical sense."]). For example, when researchers study the anti-thrombotic (anti-clotting) effects of aspirin, they use a composite endpoint of biologically related, clot-induced events such as non-fatal heart attack, non-fatal stroke, and vascular death. Markel Decl., Ex. 11 at 82 (Antiplatelet Trialists' Collaboration, BRIT. MED. J., 1994;308:81-106).[3] This composite endpoint, known as the Antiplatelet Trialists' Collaboration or "APTC" endpoint, was developed by a renowned group of cardiologists and thrombosis experts, and it is used regularly today by researchers evaluating the potential thrombotic effects of drugs. *See* Markel Decl., Ex. 8 at 34-35 (Furberg Dep.).

A researcher conducting a post hoc analysis also must rely on medical doctors in the relevant field to choose a clinically valid endpoint—before looking at the trials' results—and then apply that endpoint consistently across all the trials being reviewed, rather than changing the endpoint definition from trial to trial depending on the results. Systematically applying a clinically valid endpoint prevents an unscrupulous reviewer from constructing a composite endpoint from disparate outcomes to create a statistically significant difference in events,

[3] Certain heart attacks and strokes are caused by clots that restrict the flow of blood to the heart or brain. Those events commonly are referred to as "thromboembolic" or "thrombotic" events to distinguish them from non-thrombotic cardiovascular problems that are not induced by blood clots, which include conditions such as abnormal heart rhythms (known as arrhythmias) or the inability of the heart to pump enough blood (known as congestive heart failure). For the sake of clarity, this brief will use the term "thrombotic events" to refer to heart attacks and strokes.

regardless of whether the outcomes are related clinically.[4] Such an approach also protects against the temptation to change the endpoint definition from trial to trial in order to contrive an apparent pattern of numerical imbalances that support the reviewer's predetermined conclusions. Plaintiffs' experts concede that this practice is inappropriate and scientifically invalid. *See* Markel Decl., Ex. 12 at 228 (Kronmal Dep. ["[Y]ou can't do a meta-analysis where you use one end point for one study and another end point for another. That doesn't even make any sense."]); Markel Decl., Ex. 8 at 83, 85-86 (Furberg Dep.).

3. Collect and Classify the Endpoint Events Using Reliable Methods

Qualified medical doctors must collect data relevant to the endpoint in a way that is reliable and consistent. During a clinical trial, patient events are reported by physicians who serve as field investigators at various study locations. As a result, events may be reported in different ways by different field investigators, and even different ways by the same doctor at different times. To eliminate these inconsistencies, many trials have what are called adjudication committees, which are groups of medical experts who specialize in the outcomes of interest and review all of the patient reports without knowing whether the patients are taking the medication being tested or placebo pills (a process known as "blinding") using pre-specified, written criteria to ensure that all events are defined, counted, and classified consistently.[5] For example, where an aspirin trial analyzes whether aspirin decreases the risk of heart attacks and other clotting events, a committee of cardiologists review both the heart attacks to ensure that they are, in fact, heart attacks, as well as other patients' records to ensure that additional heart attacks were not misclassified as the wrong condition or missed entirely by investigators in the field. Markel Decl., Ex. 11 at 82-83 (Antiplatelet Trialists' Collaboration, BRIT. MED. J. 1994;308:81-106).

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[4] *See* Markel Decl., Ex. 5 at 42 (EVALUATING CLINICAL RESEARCH [warning that "[r]ed flags may include the use of unusual or illogical composites, *e.g.*, outcome measures that have uncertain clinical relevance."]); Markel Decl., Ex. 10 at 301 (Furberg & Morgan, STAT. MED. 1987;6:295-303); *see also* Markel Decl., Ex. 8 at 78-80 (Furberg Dep.).

[5] *See* Markel Decl., Ex. 13 at 63 (Madigan Dep.); Markel Decl., Ex. 8 at 105 (Furberg Dep.); Markel Decl., Ex. 12 at 129 (Kronmal Dep.); Markel Decl., Ex. 7 at 232-33, 769-70, 781 (Furberg Dep., *Haslam v. Pfizer*); Markel Decl. Ex. 5 at 51 (EVALUATING CLINICAL RESEARCH).

Where a researcher collects events from a variety of clinical trials for a post hoc analysis, he or she must take several measures to avoid invalid and unreliable results. First, the post hoc researcher must gather complete and accurate information about the adverse events that fulfill the chosen endpoint definition. Generally, there are three sources of information on clinical trials: (1) published articles in medical journals; (2) study reports, often thousands of pages long, that manufacturers file with FDA; and (3) electronic data files (known as SAS data files), which contain certain patient level data. Ideally, a researcher conducting a post hoc analysis should review all three sources to capture all trials and the occurrence of all confirmed adverse events that fulfill the endpoint definition in those trials. *See* Markel Decl., Ex. 8 at 63-65 (Furberg Dep. [noting that a review based only on published literature is particularly suspect]).

Second, the researcher should employ an objective process for selecting trials to include in the analysis so as not to be influenced by the results; otherwise, where the person deciding whether to include studies knows the results, the overview's conclusions are "highly questionable." Markel Decl., Ex. 10 at 299 (Furberg & Morgan, STAT. MED. 1987;6:295-303).

Third, inconsistencies in the criteria used to diagnose medical outcomes that may be present in a single trial can be even greater across multiple trials, which may have been conducted at different times by different investigators with different diagnostic criteria. Thus, it is especially important in a post hoc review of many trials to extract data from the most reliable source of original patient information and to classify events according to accepted diagnostic criteria for the medical condition of interest.[6] The post hoc investigator should make sure that no events were missed or misclassified in any of the trials being reviewed, which requires establishing rules for how patients' medical outcomes will be collected and classified across the entire dataset (*e.g.*, by creating medically valid, written rules to adjudicate the events across trials). *See* Markel Decl., Ex. 7 at 769-70, 781 (Furberg Dep., *Haslam v. Pfizer*). A researcher

[6] *See* Markel Decl., Ex. 13 at 63-65 (Madigan Dep.); Markel Decl., Ex. 7 at 781 (Furberg Dep., *Haslam v. Pfizer*); Markel Decl. Ex. 3 at 79, 309 (Bennett Dep., *In re Bextra*); Markel Decl., Ex. 5 at 25 (EVALUATING CLINICAL RESEARCH); Markel Decl., Ex. 4 at 311 (FUNDAMENTALS OF CLINICAL TRIALS).

should not, however, modify the criteria or reclassify selective events to reach a desired conclusion. *See* Markel Decl., Ex. 5 at 11-12, 43 (EVALUATING CLINICAL RESEARCH); *see also* Markel Decl., Ex. 8 at 159 (Furberg Dep.).

4. Use Reliable Statistical Methods to Evaluate the Results

Finally, after qualified medical doctors have collected and classified events that are specified in advance according to an endpoint that has an accepted biological basis, statisticians help evaluate whether differences between groups are due to the play of chance. *See* Markel Decl., Ex. 5 at 107 (EVALUATING CLINICAL RESEARCH); *Ref. Man.* at 87, 115. To do that, statisticians conduct tests using a pre-specified probability value or "*p*-value."[7] If the difference exceeds the pre-specified *p*-value, then the result is said to be "statistically significant"—that is, the result is unlikely to be the result of random sampling error or mere chance. *See Ref. Man.* at 396; Markel Decl., Ex. 5 at 107 (EVALUATING CLINICAL RESEARCH). Statistical significance does not establish a causal relationship, only that the two events may be associated.[8] Choosing the *p*-value in advance prevents an unscrupulous reviewer from modifying the *p*-value threshold after reviewing the results in order to declare that a result is statistically significant.[9] *See* Markel Decl., Ex. 5 at 11-12 (EVALUATING CLINICAL RESEARCH).

D. Accepted Methods Of Interpreting Clinical Trial Results

Even where a researcher specifies a valid clinical question in advance, systematically applies a clinically valid endpoint, reliably collects and classifies the relevant medical outcomes, and uses reliable statistical methods to evaluate the play of chance, qualified medical experts still

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[7] A *p*-value functions as an error rate by indicating that probability that the observed difference will arise by chance alone if the trial is repeated. *See* Markel Decl., Ex. 5 at 141 (EVALUATING CLINICAL RESEARCH). A *p*-value of 0.05 means that there is a 5% chance that the result seen in the trial was due to chance alone (*i.e.*, a 5% error rate). *See Ref. Man.* at 358-59. The most conventional *p*-value is < 0.05. Markel Decl., Ex. 2 at 6 (Kronmal Rep.).

[8] *See* Markel Decl., Ex. 8 at 136-37 (Furberg Dep.); Markel Decl., Ex. 12 at 184 (Kronmal Dep.); Markel Decl., Ex. 68 at 212, 261 (Kronmal Dep., *McFarland v. Merck*).

[9] If a post hoc researcher compares enough variables between two treatment groups, some of the comparisons may appear nominally statistically significant by chance alone, when in fact no difference exists, known as a "multiple comparison" problem. *Ref. Man.* at 166. Markel Decl., Ex. 4 at 124, 339 (FUNDAMENTALS OF CLINICAL TRIALS).

must decide whether to extrapolate the results to patients who did not participate in the trial. Whether interpreted prospectively or retrospectively, clinical trial data should only be interpreted to predict an effect associated with the specific medication, population and dose involved in the study. Any extrapolation beyond that requires a "leap of faith" that may be unwarranted.[10]

1. Extrapolating from Other Medications

First, a researcher should not extrapolate an effect seen with one medication to another simply because they belong to the same class of drugs. While some of Plaintiffs' experts make such assumptions based on a so-called class effect,[11] Plaintiffs' experts concede that the concept of a class effect is not defined, lacks objective criteria, and improperly assumes that medications have certain effects based simply on membership in a class even though they may have clinically important differences in safety.[12] In particular, it is inappropriate to extrapolate data from one form of administration of a medication to another – for example, from an intravenous administration to oral pills. *See* Markel Decl., Ex. 4 at 181-82 (FUNDAMENTALS OF CLINICAL TRIALS); Markel Decl., Ex. 14 at IV-18 (Furberg, CLIN. CARDIOL. 2000;23;7 Suppl. 4:IV15-19).

2. Extrapolating from Other Populations

In addition, extrapolation to populations not included in a study may be inappropriate if the patients have different biological or physiological characteristics.[13] Extrapolating the results

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[10] *See* Markel Decl., Ex. 5 at 131 (EVALUATING CLINICAL RESEARCH); Markel Decl., Ex 4 at 38 (FUNDAMENTALS OF CLINICAL TRIALS); Markel Decl., Ex. 15 at 570 (Furberg, HEART 2002; 87:570-74).

[11] *See* Markel Decl., Ex. 1 at 47-48 (Furberg Rep.); Markel Decl., Ex. 97 at 1-2 (Madigan Rep.); Markel Decl., Ex. 9 at 3-5 (Bennett Rep.); Markel Decl., Ex. 61 at 8-14 (Baruch Rep.) Markel Decl., Ex. 102 at 4-5 (Jewell Rep.).

[12] *See* Markel Decl., Ex. 3 at 279-80 (Bennett Dep., *In re Bextra* ["If you want to study Celebrex, I think you can't use Vioxx data"]); Markel Decl., Ex. 7 at 282-83 (Furberg Dep., *Haslam v. Pfizer* [stating he would not combine Bextra data, Vioxx data and naproxen data to answer a research question about whether Bextra is causing harm]); *id.* at 151-53, 166-67, 444-46, 456; Markel Decl., Ex. 5 at 131 (EVALUATING CLINICAL RESEARCH ["[F]indings related to one particular drug and dose may not apply to other drugs, even within the same class."]); Markel Decl., Ex. 14 at IV-15 (Furberg, CLIN. CARDIOL. 2000;23;7 Suppl. 4:IV15-19 ["[T]he concept of 'class effect' is a term of convenience that has no universally accepted definition and subsequently should not form the basis for the practice of evidence-based medicine."]); Markel Decl., Ex. 16 at 1203 (Furberg et al., LANCET 1999;354:1202-04).

[13] *See* Markel Decl., Ex. 17 at 88 (Furberg, POSTGRADUATE MEDICINE: A QUARTER-CENTURY OF BETA BLOCKADE (1988) ["Extrapolation to subsets of patients that would not have qualified for enrollment into the trial represents a leap of faith."]); Markel Decl., Ex. 7 at 151-54 (Furberg Dep., *Haslam v. Pfizer* ["[I]n a strict sense, . . . the findings apply to the people you study. . . . So you have to extrapolate . . . some leaps are small; some are big

of a clinical trial to the general patient population is particularly problematic when the trial involves a special population, such as patients undergoing surgery. Markel Decl., Ex. 4 at 341 (FUNDAMENTALS OF CLINICAL TRIALS [questioning whether an intervention involving a special procedure, such as surgery, is likely to produce the same response outside the trial setting]); Markel Decl., Ex. 3 at 328-29 (Bennett Dep., *In re Bextra* [admitting one cannot "extrapolate findings from [bypass surgery] data to people taking the drug in the real world for arthritis"]).

3. Extrapolating from Higher Doses

Finally, dose is a relevant factor to consider in interpreting the results of clinical trials since medications typically produce more side effects at higher doses. Markel Decl., Ex. 7 at 142-43 (Furberg Dep., *Haslam v. Pfizer*). "Dose is the single most important factor to consider in evaluating whether an alleged exposure caused a specific adverse effect. Indeed . . . '[a]ll substances are poisonous – there is none which is not; the dose differentiates a poison from a remedy.'" David L. Eaton, *Scientific Judgment and Toxic Torts—A Primer in Toxicology for Judges and Lawyers*, 12 J. L. & Pol'y 5, 11 (2003) (citation omitted). For most medicines, there exists an exposure to the medicine that does not cause the effect of interest. *See id.* at 15. Thus, it may be unclear to what degree an increased risk extends to patients taking lower doses when specific studies have not been conducted using those lower doses.[14]

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and questionable."]); Markel Decl., Ex. 4 at 37 (FUNDAMENTALS OF CLINICAL TRIALS ["As long as selection of participants into a trial occurs, they must be regarded as special. Therefore investigators have the problem of generalizing from participants actually in the trial to the study population and then to the population with the condition."]); Markel Decl., Ex. 18 at 304-05 (Jewell Dep., *In re Bextra* [acknowledging that extrapolating outside the population studied requires qualifications other than statistics]).

[14] *See* Markel Decl., Ex. 20 (Furberg et al., CIRCULATION 2005; 111:249); Markel Decl., Ex. 23 at 169 (Transcript of Arthritis Advisory Committee ["Ad. Comm. Tr."], Feb. 18, 2005 [Furberg admitting the statistical evidence of increased risk of thrombotic events with Celebrex "is in a select population, in a select dose"]); Markel Decl., Ex. 5 at 116 (EVALUATING CLINICAL RESEARCH ["A critical determinant of efficacy is drug dose."]); Markel Decl., Ex. 6 at 89 (Furberg Dep., *Valenzuela v. Warner-Lambert*); Markel Decl., Ex. 3 at 220-21 (Bennett Dep., *In re Bextra*).

II. APPLICATION OF UNDISPUTED METHODS TO CELEBREX AND BEXTRA

A. Celebrex Is The Only Selective COX-2 Inhibitor Still On The Market

1. Celebrex Pre-Approval Studies

Celebrex is a type of non-steroidal anti-inflammatory drug ("NSAID") approved to treat the symptoms of osteoarthritis, rheumatoid arthritis, and other conditions. Markel Decl., Ex. 21 at 3 (Celebrex Label, Dec. 2008). NSAIDs work by inhibiting production of an enzyme called cyclo-oxygenase, or COX. There are two forms of the COX enzyme in the body: COX-1, a "housekeeping" enzyme that is important for protection of the stomach lining and regulation of the kidneys and other bodily functions; and COX-2, an enzyme which plays a key role in causing pain and inflammation. NSAIDs that inhibit both COX-1 and COX-2 commonly are referred to as "non-selective" NSAIDs and include ibuprofen (Advil and Motrin) and naproxen (Aleve), while NSAIDs that primarily target COX-2 commonly are referred to as "selective" COX-2 inhibitors (or simply COX-2 inhibitors) and include Celebrex, Vioxx, and Bextra.

By blocking the "housekeeping" COX-1 enzyme, non-selective NSAIDs cause serious side effects such as stomach ulcers, kidney dysfunction, internal bleeding and interference with platelet function.[15] Given those adverse health effects, scientists began to look for ways to provide effective pain relief with less gastrointestinal risk. In the early 1990s, researchers at Searle developed a new compound that blocked the COX-2 enzyme without interfering with the gastrointestinal protection of the COX-1 enzyme. It was hoped that patients suffering from the chronic pain of arthritis would tolerate this new drug better and suffer fewer side effects. The compound came to be known as Celebrex (also known by its generic name, celecoxib).

The Celebrex development process took nearly six years. The research team spent more than a year synthesizing and testing more than 2,500 compounds before identifying the Celebrex molecule. They spent another year conducting 34 laboratory and animal studies and another

[15] Indeed, prior to the introduction of Celebrex, it had been estimated that more than 100,000 patients were hospitalized yearly due to the side effects of non-selective NSAIDs, and that approximately 16,500 patients died from gastrointestinal complications. Markel Decl., Ex. 22 (Singh & Ramey, J. RHEUM. 1998;25(Supp. 51):8-16).

three years conducting 51 clinical trials involving more than 13,000 unique patients, over 9,400 of whom took Celebrex (approximately 2,300 of whom took Celebrex for a year or more), for a total of more than 3,200 patient-years of safety data.[16] In 1999, when Celebrex came to market, it was the most studied arthritis medication in history.

The data show that Celebrex patients suffered fewer ulcer complications and less nausea, abdominal pain, and upset stomach than patients taking non-selective NSAIDs. Markel Decl., Ex. 25 at 372, 382 (Celecoxib Integrated Summary of Safety, June 5, 1998). The gastrointestinal advantages of Celebrex have been confirmed over time. Markel Decl., Ex. 21 at 12 (Celebrex Label, Dec. 2008). At the time of its approval, the complete body of scientific data showed no evidence that patients taking Celebrex have an increased risk of heart attacks or strokes compared to patients taking other NSAIDs or no medication at all. Markel Decl., Ex. 26 at 11 (James Witter, *Celebrex Medical Officer Review*, NDA No. 20-998, July 8, 1998).

2. Celebrex Post-Approval Studies

Following approval, scientists continued to study the health of patients taking Celebrex. The accumulating data continued to show no evidence of an increased thrombotic risk. In 2000, Pfizer completed a large, highly publicized study known as CLASS. CLASS involved 7,968 arthritis patients, 3,987 of whom took Celebrex at 800 milligrams ("mg") daily (four times the recommended daily osteoarthritis dose of 200 mg) every day for up to 15 months who were compared to patients taking standard doses of non-selective NSAIDs such as prescription strength Motrin. CLASS showed no evidence of an increased thrombotic risk for patients taking Celebrex compared to patients taking the non-selective NSAIDs, which at the time were thought by the medical and scientific community to carry no increased risk of thrombotic events. Markel Decl., Ex. 21 at 12 (Celebrex Label, Dec. 2008); Markel Decl., Ex. 8 at 123 (Furberg Dep.).

[16] *See* Markel Decl., Ex. 23 at 380 (Transcript of Arthritis Advisory Committee ["Ad. Comm. Tr."], Feb. 16, 2005); Markel Decl., Ex. 25 at 35, 52, 54 (Celebrex Integrated Summary of Safety); Markel Decl., Ex. 24 at 14 (Celebrex Label, Jan. 1999).

At about the same time, Merck received the results of a similar Vioxx study called VIGOR, which showed that patients taking Vioxx experienced approximately four times more heart attacks than patients taking prescription strength Aleve, resulting in a statistically significant increased risk with Vioxx. *See* Markel Decl., Ex. 27 (Bombardier et al., NEW ENGL. J. MED., 2000;343:1520-28); Markel Decl., Ex. 31 at 8, Table 3 (Vioxx Label, Apr. 2002). Thereafter, FDA revised the labels for both Celebrex and Vioxx to reflect the thrombotic results of the respective CLASS and VIGOR trials for each medication.[17]

After the CLASS trial, Pfizer continued to study the health of Celebrex patients, and the data continued to show no evidence that Celebrex carried an increased risk of thrombotic events. By the fall of 2004, the health of Celebrex patients had been studied in clinical trials involving more than 25,000 arthritis patients, more than 10,000 of whom took Celebrex every day for at least six months and up to two years. None of those studies revealed a statistically significant increase in the risk of thrombotic events. Markel Decl., Ex. 28 at 16 (Pfizer Inc.'s Advisory Committee Briefing Document, *Celecoxib and Valdecoxib Cardiovascular Safety*, Jan. 12, 2005 ["Pfizer Briefing Doc."]). At the same time, Pfizer, the National Institutes of Health ("NIH"), and other independent scientists were conducting dozens of promising experimental, high-dose clinical trials to see whether Celebrex could help prevent or attenuate diseases such as colon cancer, breast cancer, and Alzheimer's disease.

3. Withdrawal of Vioxx from the Market

On September 30, 2004, Merck withdrew Vioxx from the world market after another Vioxx study, APPROVe, showed that patients taking Vioxx experienced a statistically significant two-fold increase in confirmed thrombotic events compared to patients taking

[17] *See* Markel Decl., Ex. 30 at 21 (Celebrex Label, June 2002 [noting "there were *no differences* between the CELEBREX, diclofenac, or ibuprofen treatment groups" for "investigator-reported serious cardiovascular thromboembolic adverse events"] [emphasis added]); Markel Decl., Ex. 31 at 12 (Vioxx Label, Apr. 2002 [noting "the risk of developing a serious cardiovascular thrombotic event was *significantly higher* in patients treated with Vioxx"] [emphasis added]).

placebo. Markel Decl., Ex. 29 (Bresalier et al., N. ENGL. J. MED. 2005;352-63). This statistically significant difference replicated the results seen in the earlier VIGOR study.

After the withdrawal of Vioxx, independent scientists also performed a series of observational studies comparing patients who took Vioxx or Celebrex to patients who took non-selective NSAIDs or no NSAID at all. Those studies, consisting of more than 80,000 arthritis patients who took Celebrex at all doses prescribed in the community, supported the clinical trial data and consistently showed no increased risk of thrombotic events with Celebrex, but did show an increased risk with Vioxx.[18] Dr. David Graham, Medical Officer at FDA's Center for Drug Evaluation and Research ("CDER"), conducted one of these observational studies and wrote in an internal FDA memorandum: "[W]e estimate that the increased [Vioxx] risk observed in this study would yield an excess of 27,785 cases of [acute myocardial infarction] and [sudden cardiac death] in the US over the years 1999-2003 . . . These would have been avoided had [Celebrex] been used instead of [Vioxx]." Markel Decl., Ex. 32 at 10 (Graham Memo to Seligman, Sept. 30, 2004). The observational studies demonstrating the safety of Celebrex compared to Vioxx also were consistent with head-to-head clinical trials and observational studies, which repeatedly showed that Vioxx and Celebrex had significantly different effects,[19] as well as other studies that evaluated cardiovascular differences between Celebrex and Vioxx.[20]

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[18] Four of the five observational studies showed an increased cardiovascular risk with Vioxx, while none showed an increased risk with Celebrex. Markel Decl., Ex. 33 (Graham et al., Lancet 2005;365:475-81); Markel Decl., Ex. 34 (Hippisley-Cox et al., Brit. Med. J., 2005;330:1366-1372); Markel Decl., Ex. 35 (Mamdani et al., Arch. Intern. Med. 2003;163:481-86); Markel Decl., Ex. 36 (Mamdani et al., Lancet 2004;363:1751-1756); Markel Decl., Ex. 37 (Ray et al., Lancet 2002;360:1071-73); Markel Decl., Ex. 38 (Solomon D. et al., Circulation 2004;109:2068-73).

[19] For articles describing the head-to-head trials, see Markel Decl., Ex. 39 (Sowers et al., ARCH. INTERN. MED. 2005;165:161-168); Markel Decl., Ex. 40 (Whelton et al., AM. J. THER. 2001;8:85-95); Markel Decl., Ex. 41 (Whelton et al., AM. J. CARDIOL. 2002;90:959-963). For articles describing the observational studies, see Markel Decl., Ex. 42 (Hudson et al., BRIT. MED. J. 2005;330:1370-1375); Markel Decl., Ex. 36 (Mamdani et al., LANCET 2004;363:1751-1756); Markel Decl., Ex. 43 (Solomon D. et al., HYPERTENSION 2004;44:140-145); Markel Decl., Ex. 44 (Wolfe et al., J. RHEUMATOL. 2004;31:1143-1151).

[20] Those studies include: (1) research showing that Vioxx, but not Celebrex, increases oxidative stress in the arteries, which is a potential contributing factor to plaque instability and clot formation, *see* Markel Decl., Ex. 45 (Walter et al., ATHEROSCLEROSIS 2004:177:235-243); and (2) studies showing that Celebrex, but not Vioxx, has cardio-beneficial effects, including the inhibition of tissue factor (a harmful substance), the improvement of endothelial (lining of the vessel) function, the reduction of oxidative stress, and other effects that are thought to reduce the development or progression of atherosclerosis. *See* Markel Decl., Ex. 46 (Steffel et al., CIRCULATION

At the same time, independent data safety monitoring committees overseeing the ongoing experimental, high-dose studies of Celebrex for the prevention of cancer and Alzheimer's disease reviewed the data from those clinical trials in light of the Vioxx withdrawal and found no reliable evidence that Celebrex increased the risk of heart attacks and strokes.[21]

4. APC, PreSAP and ADAPT Studies

On December 16, 2004, however, the National Cancer Institute ("NCI") suddenly halted the Adenoma Prevention with Celecoxib trial ("APC"). That trial, which studied patients taking two (400 mg daily) and four (800 mg daily) times the recommended daily osteoarthritis dose of Celebrex (200 mg daily) every day for almost three years, showed that patients taking high doses of Celebrex experienced a higher rate of heart attacks and strokes compared to patients taking placebo pills. Markel Decl., Ex. 49 at 1071 (Solomon S. et al., N. ENGL. J. MED. 2005;352:1071-80). The differences were statistically significant, though the difference between patients taking two times (400 mg daily) the approved osteoarthritis dose and those taking placebo pills was only borderline significant. *Id.* at 1075 (reflecting barely significant confidence intervals).[22]

Immediately, FDA announced that this was the first time researchers saw a statistically significant increase in thrombotic events with Celebrex compared to patients taking placebo: "**Previous large studies of Celebrex, including clinical trials and epidemiology studies, have not suggested the sort of [cardiovascular] risk found in the NCI polyp study**." Markel Decl., Ex. 50 (FDA Statement on the Halting of a Clinical Trial of the Cox-2 Inhibitor Celebrex, Dec. 17, 2004 [emphasis added]). In fact, after reviewing all the Celebrex data, Plaintiffs' experts

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2005;111:1685-1689); Markel Decl., Ex. 47 (Hermann et al., CIRCULATION 2003;108:2308-11); Markel Decl., Ex. 48 (Klein et al., CARDIOVASC. RES. 2007;75:390-97).

[21] *See* Markel Decl., Ex. 51 at 1 (Memo from Monica Bertagnolli to Pfizer re: APC Trial Cardiovascular Safety Review, Oct. 15, 2004); Markel Decl., Ex. 52 at 1 (National Institutes of Health Press Release, *Use of Non-Steroidal Anti-Inflammatory Drugs Suspended in Large Alzheimer's Disease Prevention Trial*, Dec. 20, 2004 [stating that "no significant increase in risk for celecoxib was found in this trial"]).

[22] A confidence interval, which is another way to express statistical significance, is expressed as a range of values that are calculated at some level of probability to contain the true value. For instance, a 95% confidence interval means that there is a 95% probability that the true value falls within the range. *See Ref. Man.* at 161, 360-61.

Joel Bennett and Richard Kronmal reached the same conclusion – that the APC trial results in December 2004 showed the first statistically significant difference in the rate of heart attacks or strokes between patients taking any dose of Celebrex and those taking either a placebo pill or an NSAID like prescription Motrin or Aleve. Markel Decl., Ex. 3 at 385-86 (Bennett Dep., *In re Bextra*); Markel Decl., Ex. 12 at 345-46 (Kronmal Dep.).[23]

Moreover, in contrast with APC, two other high-dose, long-term, disease prevention trials – one other studying the preventive effects of Celebrex on colon cancer (PreSAP) and the other studying the preventive effects on Alzheimer's disease (ADAPT) – showed no statistically significant differences in thrombotic events between patients taking high doses of Celebrex and those taking placebo pills. In PreSAP, 1561 patients took two times the osteoarthritis dose of Celebrex every day for three years and the results showed no statistically significant difference. Markel Decl., Ex. 53 at 886 (Arber et al., N. ENGL. J. MED. 2006;355:885-95). In the ADAPT trial, 2528 patients took twice the osteoarthritis dose every day for three years and the results showed that patients taking high doses of Celebrex actually experienced *lower* rates of heart attack than patients taking placebo pills, though the difference was not statistically significant. Markel Decl., Ex. 54 (ADAPT Research Group, PLOS CLIN. TRIALS 2006;1(7): e33).

FDA recognized that the PreSAP and ADAPT results were inconsistent with the APC results. Markel Decl., Ex. 55 at 4-5 (John K. Jenkins & Paul J. Seligman, *Analysis and Recommendations for Agency Action Regarding Non-Steroidal Anti-Inflammatory Drugs and Cardiovascular Risk*, Apr. 6, 2005 ["FDA Decision Mem."] [noting that the APC results "were not replicated, however, in the nearly identical" PreSAP trial and that ADAPT "also does not appear to have shown an increased risk"]); *id.* at 9 (noting that "a nearly identical long-term placebo-controlled trial (the PreSAP trial) and a similarly sized placebo-controlled trial in patients at increased risk for Alzheimer's disease did not replicate [the APC] findings").

[23] Even after the APC data became available, Bennett wrote that the cardiovascular risk of COX-2s other than Vioxx "remains to be established." Markel Decl., Ex. 56 at 1835 (WILLIAMS HEMATOLOGY (7th ed., 2007)).

5. FDA's Analysis of the Celebrex Data

On February 18, 2005, FDA convened a joint meeting of the Arthritis and Drug Safety and Risk Management Advisory Committees ("the Advisory Committee") to review all available data and to try to answer the public health question of whether and to what extent NSAIDs increase the risk of thrombotic events such as heart attack and stroke. The Advisory Committee heard presentations from the NSAID manufacturers and external experts. All of the Celebrex clinical trials that Plaintiffs rely on here – as well as the available observational study data – were reviewed and discussed at the meeting.[24]

Based on the totality of available data, the Advisory Committee voted almost unanimously to keep Celebrex on the market. Markel Decl., Ex. 57 at 11 (FDA Ad. Comm. Minutes [voting 31 to 1 that the overall risk-benefit profile of Celebrex supported keeping it on the market]). It also found no evidence of an increased risk at the most commonly used dose of 200 mg daily, a possible increased risk at 400 mg daily, and an increased risk at 800 mg daily. *Id.*

On April 6, 2005, following the hearing, FDA issued a memorandum setting forth its recommendations and analysis. Markel Decl., Ex. 55 (FDA Decision Mem.). FDA began by defining the relevant public health question; namely, whether and to what extent the various NSAIDs increase the risk of thrombotic events. *Id.* at 1. This was based in part on the Vioxx trials, VIGOR and APPROVe, and APC, all of which showed a statistically significant difference in thrombotic events like heart attack and stroke. *Id.* at 8-9. As part of its analysis, FDA also evaluated the biological theory known interchangeably as the "FitzGerald," "COX-2 selectivity,"

[24] *See* Markel Decl. Ex. 57 at 9 (FDA Summary Minutes for Feb. 16-18, 2005 Ad. Comm. Mtg. ["Ad. Comm. Minutes"]); Markel Decl., Ex. 55 at 7 (FDA Decision Mem.); Markel Decl. Ex. 58 (Presentation by Dr. James Witter, Lead Medical Officer at FDA's CDER, Feb. 16, 2005); Markel Decl., Ex. 59 (*Review of Epidemiologic Studies on Cardiovascular Risk With Selected NSAIDs*, Presentation by Dr. David Graham, Medical Officer at CDER, Feb. 17, 2005).

or "imbalance" hypothesis, which postulates that selective COX-2 inhibitors promote clotting and thus increase the risk of thrombotic events. *Id.* at 8.[25]

To answer the question regarding thrombotic risk, FDA chose an endpoint widely accepted by medical doctors in the cardiovascular community—the APTC composite endpoint, which includes non-fatal heart attack, non-fatal stroke, and vascular death. Markel Decl., Ex. 55 at 4 (FDA Decision Mem.). FDA chose this endpoint because it is "a widely accepted endpoint in assessing the benefits and risks of a drug for [cardiovascular] outcomes." *Id.* Indeed, the APTC endpoint has been used repeatedly to analyze thrombotic events in other settings, as well as by highly regarded COX-2 researchers on whose analyses Plaintiffs' experts rely. *See, e.g.*, Markel Decl., Ex. 60 at 1303 (Kearney et al., BRIT. MED. J., 2006;332(7553):1302-08 ["Kearney"] [using APTC endpoint as primary measure of cardiovascular safety]).[26]

FDA then applied the APTC endpoint consistently across all Celebrex clinical trials, including each trial relied on by Plaintiffs here. *See* Markel Decl., Ex. 55 at 4-5 (FDA Decision Mem.). FDA's evaluation of the Celebrex data included a trial known as "Alzheimer's 001," which involved 425 patients with Alzheimer's disease and compared those taking Celebrex at a dose of 200 mg twice daily (two times the approved osteoarthritis dose) for one year to patients taking placebo pills. While several of Plaintiffs' experts now cite that study as statistically significant evidence that was available before the APC trial, FDA found no statistically significant increased risk of thrombotic events in the trial. Markel Decl., Ex. 55 at 4-5 (FDA

[25] *See also* Markel Decl., Ex. 61 at 11 (Baruch Rep. [adopting the hypothesis]); Markel Decl., Ex. 3 at 118 (Bennett Dep., *In re Bextra* [agreeing with the hypothesis]); Markel Decl., Ex. 12 at 51 (Kronmal Dep. [acknowledging the hypothesis played a role in his selection of endpoints]). The hypothesis is named after Garrett FitzGerald, a researcher at the University of Pennsylvania who authored several publications regarding the hypothesis.

[26] In fact, Plaintiffs' own experts have used the APTC endpoint themselves outside of this litigation. *See, e.g.*, Markel Decl., Ex. 5 at 89 (EVALUATING CLINICAL RESEARCH ["Combining events of similar severity such as cause-specific mortality, non-fatal myocardial infarction and stroke is generally accepted."]); Markel Decl., Ex. 20 (Furberg et al., CIRCULATION 2005;111(3):249); Markel Decl., Ex. 62 (Folsom et al. [Richard Kronmal co-author], ARCH. INTERN. MED. 2008;168(12):1333-1339); Markel Decl., Ex. 63 (Smith et al. [Richard Kronmal co-author], ARCH. INTERN. MED. 2002;162(2):209-216); Markel Decl., Ex. 8 at 34-35 (Furberg Dep. [referencing his CIRCULATION article that used a combined endpoint of heart attack and stroke, and admitting "I've done it myself"]).

Decision Mem. [stating Alzheimer's 001 "did not demonstrate a significantly increased risk of serious adverse [cardiovascular] events"]). FDA's determination was consistent with the conclusions of the investigators who conducted the Alzheimer's 001 trial, a meta-analysis cited by Plaintiffs' experts, and the U.S. Securities & Exchange Commission ("SEC"), which investigated all disclosure issues related to Alzheimer's 001 and found no violations.[27] Finally, the NIH-sponsored ADAPT trial, a subsequent Celebrex trial that was independent, larger, and in the same Alzheimer's population, showed no increased risk of thrombotic events. *See* Markel Decl., Ex. 54 at 007 (ADAPT Research Group, PLoS CLIN. TRIALS 2006;1(7): e33).[28]

With respect to CLASS, which compared patients taking four times the osteoarthritis dose of Celebrex to patients taking standard doses of two non-selective NSAIDs, FDA stated: "No differences were observed for serious adverse [cardiovascular] events between celecoxib and the two non-selective NSAID comparators in this trial." Markel Decl., Ex. 55 at 5 (FDA Decision Mem.). That determination echoed FDA's labeling decision in 2001, in which FDA concluded that there were "no differences" between Celebrex and the non-selective NSAIDs with respect to thrombotic events. Markel Decl., Ex. 30 at 21 (Celebrex Label, June 2002).

Indeed, FDA identified APC as the only study showing a statistical association between Celebrex use and the incidence of thrombotic events. Markel Decl., Ex. 55 at 4-5 (FDA Decision Mem.). FDA's conclusion that APC was the only trial that showed a statistically significant difference in thrombotic events is consistent with the conclusions of Plaintiffs' own experts Bennett and Kronmal, who testified that there was no reliable evidence of a thrombotic risk with Celebrex until the APC results became available in December 2004.[29] FDA's finding

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[27] Markel Decl., Ex. 64 at 19 (Soininen at al., DEMENT. GERIATR. COGN. 2007;23:8-21); Markel Decl., Ex. 60, at 1305 (Kearney); Markel Decl., Ex. 65 at 1 (Ltr. from SEC to Ethan Posner, Aug. 16, 2006).

[28] In addition, no qualified cardiologist retained by Plaintiffs disputes the methodologies of the three defense cardiologists who blindly adjudicated the cardiovascular events in the Alzheimer's 001 trial. *Compare* Markel Decl., Ex. 61 *passim* (Baruch Rep.) *with* Markel Decl., Ex. 66 at 22 (Weintraub Rep.).

[29] *See* Markel Decl., Ex. 67 at 182 (Bennett Testimony, Hearing in *In re Bextra*, Oct. 9, 2007); *see also* Markel Decl., Ex. 3 at 385-86. ["I think the concern (about Celebrex's thrombotic risk) was raised in 2004, the end of 2004"] (Bennett Dep., *In re Bextra*); *id.* at 107 (admitting that the results of APC never have been replicated in any other clinical trial); Markel Decl., Ex. 12 at 345-46 (Kronmal Dep.).

also is in accord with the findings of Judge Charles R. Breyer of the U.S. District Court for the Northern District of California who, after reports and testimony from eleven experts, exhaustive briefing, and extensive hearings, concluded that APC was the only Celebrex trial to demonstrate a statistically significant increase in thrombotic risk. *See In re Bextra*, 524 F. Supp. 2d at 1181-82.

FDA also analyzed the Celebrex observational studies and found no evidence that patients taking Celebrex are at any greater risk of a heart attack or stroke. *See* Markel Decl., Ex. 55 at 7 (FDA Decision Mem.). Lastly, FDA gave no weight or credibility to the Plaintiffs' "imbalance" hypothesis, explicitly finding that it is not supported by the clinical data. *Id.* at 8.

Based on precautionary public health principles, FDA did find that APC furnished enough evidence to conclude for the first time that Celebrex increases thrombotic risk, "at least at some dose, with reasonably prolonged use." *Id.* at 10. At the same time, FDA determined that Celebrex was no less safe for the heart than any non-selective NSAID, including prescription Motrin or Aleve. *See id.* at 8, 10. Because Celebrex was no less safe for the heart than other NSAIDs, FDA recommended that all NSAIDs, including Celebrex, carry the same "boxed" warning of an increased risk for heart attacks and strokes. *Id.* at 14. That boxed warning notes, "CELEBREX *may* cause an increased risk of serious cardiovascular thrombotic events, myocardial infarction, and stroke, which can be fatal. *All NSAIDs may have a similar risk.*" Markel Decl., Ex. 75 at 1 (Celebrex Label, Dec. 2006 [emphasis added]).[30]

[30] Numerous courts have recognized that in evaluating the safety of medications, FDA determinations regarding safety, labeling and the like do not establish or provide a basis for an expert opinion that a medication is associated with a particular adverse event. *See Glastetter v. Novartis Pharms. Corp.*, 252 F.3d 986, 991 (8th Cir. 2001) ("The FDA evaluates pharmaceutical drugs using a different standard than the causation standard at issue in the present case"); *Rider v. Sandoz Pharms. Corp.*, 295 F.3d 1194, 1201 (11th Cir. 2002) (noting that the "risk-utility analysis" employed by the FDA "involves a much lower standard than that which is demanded by a court of law"); *Nelson v. American Home Prods. Corp.*, 92 F. Supp. 2d 954, 958 (W.D. Mo. 2000) ("The requisite proof for causation [in a court of law] must go beyond that which is required by the [FDA] for reporting adverse drug effects or re-labeling to warn of the potential for adverse drug effects"). These decisions recognize that while "[a] regulatory agency such as the FDA may choose to err on the side of caution," courts "are required by the *Daubert* trilogy to engage in objective review of evidence to determine whether it has sufficient scientific basis to be considered reliable." *Rider*, 295 F.3d at 1201. Thus, numerous courts have held that FDA action, whether in the form of revocation of a medication's approval or in the form of requiring a warning of potential adverse effects in a label, does not constitute scientifically reliable evidence of medical causation under Daubert. *See id.* ("The district court did not

6. The Totality of the Celebrex Data Today

Celebrex safety data has continued to accumulate, and still no study has replicated the statistical findings seen in the APC trial, including three additional experimental, high-dose trials sponsored by the NCI. *See* Markel Decl., Ex. 69 (Solomon S. et al., CIRCULATION 2008;117: 2104-2113). Indeed, ongoing Celebrex studies further belie any claim that patients taking approved Celebrex doses are at an increased risk of heart attack or stroke compared to patients taking NSAIDs like prescription Aleve, which Plaintiffs claim is free of increased risk.[31]

In addition, extensive observational studies have continued to show that arthritis patients taking Celebrex are at no greater risk of heart attack and stroke than patients taking no NSAID at all. For example, in a widely cited meta-analysis of observational studies led by Dr. Patricia McGettigan, on which Plaintiffs' experts rely,[32] independent researchers analyzed 11 Celebrex observational studies involving 93,000 Celebrex patients and found that patients who take Celebrex for its approved uses in real life have no greater risk of a thrombotic event than patients taking no NSAID at all or prescription Aleve, an NSAID that Plaintiffs' experts say is safe for the heart.[33] Markel Decl., Ex. 74 at 1638-39 (McGettigan et al., JAMA 2006; 296:1633-44).

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abuse its discretion in concluding that the FDA actions do not, in this case, provide scientific proof of causation"); *Newton v. Roche Labs., Inc.*, 243 F. Supp. 2d 672, 683 (W.D. Tex. 2002) ("FDA approved warnings to physicians generally are not evidence of causation"); *Lopez v. Wyeth-Ayerst Labs., Inc.*, 139 F.3d 905 (TABLE), 1998 WL 81296, at *2 (TEXT IN WESTLAW) (9th Cir. 1998) (holding that a warning required by FDA in a medication's package insert "cannot be relied upon as evidence of causation").

[31] For example, PRECISION is a large, long-term trial involving arthritis patients at high risk for thrombotic events. The study compares patients taking arthritis doses of Celebrex to patients taking either prescription Motrin or Aleve. This trial is being run by the Cleveland Clinic, one of the country's leading cardiovascular institutions. Markel Decl., Ex. 70 (Cleveland Clinic Launches Large-Scale Global Trial to Examine Cardiovascular Safety of Popular Pain Relievers, available at http://my.clevelandclinic.org/heart/news/archive/2005/painrelief12_13.aspx [last visited July 16, 2009]). If there were a consensus in the medical and scientific community that Celebrex increases the risk of heart attacks and strokes compared to prescription Motrin or Aleve, medical institutions throughout the United States ethically could not conduct that study. *See* Markel Decl., Ex. 3 at 393-94 (Bennett Dep., *In re Bextra*); Markel Decl., Ex. 7 at 368-69 (Furberg *Haslam* Dep.); Markel Decl., Ex. 12 at 135 (Kronmal Dep.).

[32] *See* Markel Decl., Ex. 73 at 1634 (Antman et al., CIRCULATION 2007;115:1634-42 [Bennett and Furberg as co-authors citing McGettigan]); Markel Decl., Ex. 9 at 3 (Bennett Rep. [citing Antman et al.]); *see id.*, App. B (citing McGettigan); Markel Decl., Ex. 3 at 249-50, 515-16, 572-73 (Bennett Dep., *In re Bextra*); Markel Decl., Ex. 1 at 7 (Furberg Rep.).

[33] *See* Markel Decl., Ex. 3 at 203 (Bennett Dep., *In re Bextra*); Markel Decl., Ex. 67 at 150-51 (*In re Bextra* Hearing Transcript, Oct. 9, 2007 [Bennett]); Markel Decl., Ex. 7 at 842 (Furberg *Haslam* Dep.).

Today, Celebrex is the only COX-2 inhibitor still on the market. In addition to treating millions of adult arthritis patients, FDA recently found Celebrex safe enough to treat children. In 2006, two years after the APC results, FDA approved Celebrex for use in children with juvenile rheumatoid arthritis. *See* Markel Decl., Ex. 75 (Celebrex Label, Dec. 2006).

B. Bextra Was Withdrawn Because Of An Increased Risk Of Serious Skin Reactions Compared To Other NSAIDs

1. Bextra Pre-Approval Studies

On January 15, 2001, after more than four years of clinical testing, G.D. Searle submitted a New Drug Application ("NDA") seeking approval to market Bextra (also known by its generic name, valdecoxib). Markel Decl., Ex. 76 at 1 (Bextra NDA Ltr.). The Bextra NDA was one of the largest applications for an arthritis medication, detailing the results of 73 clinical trials involving 14,332 unique patients, over 9,000 of whom took Bextra, for a total of 2,196 patient-years of safety data. Markel Decl., Ex. 77 at 36, 58-59, 64 (Bextra Integrated Summary of Safety).

The Bextra clinical development program evaluated several types of medical conditions, including: (1) patients experiencing chronic pain due to conditions such as osteoarthritis, rheumatoid arthritis, chronic low back pain, and cancer pain ("the chronic pain trials"); and (2) patients experiencing acute pain as a result of acute injuries or surgeries ("the acute pain trials"). Markel Decl., Ex. 28 at 46 (Pfizer Briefing Doc.). None of the chronic pain or acute pain trials showed a statistically significant increase in thrombotic risk among patients taking Bextra – at any dose – compared to patients taking another NSAID or no NSAID at all.[34] On November 16, 2001, FDA approved Bextra and concluded that it was safe and effective when used to treat the symptoms of arthritis at a dose of 10 mg once daily and primary dysmenorrhea

[34] *See* Markel Decl., Ex. 77 at 28-29 (Bextra Integrated Summary of Safety); Markel Decl., Ex. 23 at 83 (Ad. Comm. Tr., Feb. 17, 2005 [Dr. David Graham, Associate Director for Science and Medicine, Office of Drug Safety: "With valdecoxib … the information we have at this time suggests that the risk is not increased at doses of 20 mg or less."]); Markel Decl., Ex. 28 at 47, 55 (Pfizer Briefing Doc.).

(painful menstrual cramps) at a dose of 20 mg twice daily, as needed. Markel Decl., Ex. 78, at 1 (FDA Approvable Ltr. for Bextra, Nov. 16, 2001).

2. Bextra Post-Approval Studies

As with Celebrex, Pfizer continued to study the safety and efficacy of Bextra even after FDA approved it. Although post-approval safety data continued to show no reliable evidence of an increased heart attack or stroke risk, it did begin to show rare, but serious skin reactions among Bextra users, including Stevens Johnson Syndrome and toxic epidermal necrolysis syndrome ("SJS-TENS"). Markel Decl., Ex. 79 at 1 (Dear Healthcare Provider Ltr., Sept. 2002).

3. Studies of High-Dose, Experimental, Intravenous Parecoxib

On September 11, 2000, Pfizer filed a separate NDA for parecoxib, an experimental, intravenous prodrug[35] form of Bextra. *See generally* Markel Decl., Ex. 80 (Parecoxib New Drug Application, Sept. 11, 2000). FDA, however, never approved intravenous parecoxib for any clinical purpose. Markel Decl., Ex. 81 at 1 (FDA Non-Approvable Ltr., July 12, 2001).

The Parecoxib CABG-1 Trial. In connection with the parecoxib NDA, Pfizer conducted a trial among patients who needed pain relief immediately after undergoing coronary artery bypass graft ("CABG") surgery, a trial known as CABG-1. In CABG-1, which included 462 patients, one group received 80 mg daily of intravenous parecoxib for a minimum of three days, followed by 80 mg daily of oral Bextra pills – *eight times* the approved arthritis dose – for a combined total of 14 days, while the others received standard care for surgical pain. Markel Decl., Ex. 82 at 1481 (Ott et al., J. THORAC. CARDIOVASC. SURG. 2003; 125:1481-92 ["Ott"]).

Based on a pre-specified set of rules, an adjudication committee evaluated the adverse events in the study without knowing whether the subjects had taken parecoxib and oral Bextra pills or had received standard of care. *See* Markel Decl., Ex. 83 at 15 (Presentation by Dr. James Witter, Lead Medical Officer of FDA's CDER, Feb. 16, 2005). Based on that pre-specified,

[35] A prodrug is an inactive form of a medication that converts into the active form within the human body.

independently adjudicated data, the CABG-1 study showed that the patients who received intravenous parecoxib followed by oral Bextra pills at doses that were *eight times* higher than those later approved for use by arthritis patients had a statistically higher number of overall adverse events – but not of thrombotic events in particular – compared to patients who received standard of care in the study. *See id.* at 15, 19, 20. The overall increase in adverse events was driven largely by an increase in sternal wound infections (*i.e.*, infections of the wound created when the patient's chest was cut open for the surgery). *See* Markel Decl., Ex. 82 at 1488 (Ott).

The CABG-1 results showed that the incidence of thrombotic events in patients who received high-dose, experimental intravenous parecoxib followed by high-dose oral Bextra pills was numerically greater than in the group receiving standard of care, but the differences were not statistically significant. *See id.* Indeed, Plaintiffs' expert Furberg published an editorial that recognized that the thrombotic events (heart attacks, strokes, and cardiovascular deaths) from CABG-1 were not statistically significant. *See* Markel Decl., Ex. 20 at 249 (Furberg et al., CIRCULATION 2005;111:249). Certain of Plaintiffs' other experts concede that the CABG-1 results for high-dose, experimental, intravenous parecoxib did not show a statistically significant difference in thrombotic events. *See* Markel Decl., Ex. 161 at 199-201 (Baruch Dep. [admitting CABG-1 did not show a statistically significant increase in thrombotic risk]); Markel Decl., Ex. 2 at 9-10 (Kronmal Rep. [listing table showing non-statistically significant *p*-values for CABG-1 cardiovascular events]); Markel Decl., Ex. 12 at 312 (Kronmal Dep. [admitting that none of the relative risks he calculated for CABG 1 were statistically significant]).

Similarly, FDA concluded that "interpretation of these findings cannot be conclusive at this time." Markel Decl., Ex. 84 at 3 (Medical Officer Review, Nov. 7, 2001). The FDA reviewer also noted that the dose used in CABG-1 was "eightfold higher than the dose proposed for approval for the treatment of osteoarthritis" and that the arthritis population was "distinctly different than the post-operative setting." *Id.*

On July 12, 2001, FDA informed Pfizer that the parecoxib NDA was not approvable. Markel Decl., Ex. 81 at 1 (FDA Parecoxib Sodium Non-Approvable Ltr.). In particular, FDA

noted – just five months before approving oral Bextra pills without raising any concerns about thrombotic risk – that the safety of multiple doses of parecoxib had not been established because the CABG-1 study "raise[s] the *possibility*" that parecoxib is associated with an increased risk of certain thrombotic events. *Id.* at 2 (emphasis added). FDA also noted that parecoxib use was associated with hypotension – a sudden, unsafe *decrease* in blood pressure. *Id.*[36]

In an abundance of caution, Pfizer asked FDA to approve language for the Bextra label stating that Bextra "should not be used to manage pain following coronary artery bypass graft until cardiovascular risk has been stabilized, as these patients may be at higher risk for serious adverse events." Markel Decl., Ex. 85, at 5 (Ltr. from Searle to FDA, Oct. 17, 2001). FDA rejected the proposed warning and removed all mention of the CABG-1 study in the Bextra label on the grounds that the results were not definitive, particularly because the circumstances studied there—high-dose use of experimental, intravenous parecoxib followed by oral Bextra pills following CABG surgery in a class of patients with unique physiological characteristics—were not a reliable basis to evaluate the safety of Bextra pills when used as approved.[37]

The Parecoxib CABG-2 Trial. In further consultation with FDA, Pfizer initiated another study of experimental, intravenous high-dose parecoxib followed by high-dose oral Bextra pills among patients immediately after undergoing CABG surgery, a trial known as CABG-2.[38]

Even Plaintiffs' experts concede that it was ethical to conduct a second trial among patients immediately after undergoing CABG surgery. *See* Markel Decl., Ex. 7 at 247-48 (Furberg Dep., *Haslam v. Pfizer*); *see also* note 31 *supra* (noting that a second trial could not be done ethically if the first trial showed reliable evidence of increased risk). As in the CABG-1

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[36] This hypotension effect is the exact opposite of the *increase* in blood pressure that Plaintiffs' experts associate with the use of Bextra pills, which they believe may be partly responsible for its alleged increase in thrombotic risk. *See* Markel Decl., Ex. 1 at 32-33, 42-43 (Furberg Rep.); Markel Decl., Ex. 61 at 12-13 (Baruch Rep.).

[37] *See* Markel Decl., Ex. 86 at 2-3 (Minutes of Oct. 24, 2001 NDA Meeting); Markel Decl., Ex. 84 at 3 (Medical Officer Review, Nov. 7, 2001); *see generally* Markel Decl., Ex. 78 (Bextra Initial Approved Label, Nov. 16, 2001).

[38] Furberg conceded that it was ethical to conduct a second trial among patients immediately after undergoing CABG surgery. *See* Markel Decl., Ex. 7 at 247-48 (Furberg Dep., *Haslam v. Pfizer*); *see also* note 31 *supra* (noting that a second trial could not be done ethically if the first trial showed reliable evidence of increased risk).

study, an adjudication committee evaluated the adverse events based on a pre-specified set of rules and definitions without knowing whether the subjects had taken intravenous parecoxib and oral Bextra pills as opposed to placebo. Markel Decl., Ex. 87 at 1083 (Nussmeier et al., N. ENGL. J. MED. 2005; 352:1081-91 ["Nussmeier"]). Unlike the CABG-1 study, however, the CABG-2 trial involved three groups of patients: 544 who received intravenous high-dose parecoxib followed by high-dose oral Bextra pills at a dose that was *four times* higher than that approved for use by arthritis patients ("the parecoxib / oral Bextra pills group"); 544 who received placebo followed by high-dose oral Bextra pills ("the oral Bextra pills only group"); and 548 who received placebo throughout the study ("the placebo group"). *Id.* at 1084.

Based on the pre-specified, independently adjudicated data, the CABG-2 study showed that the group taking parecoxib was at an increased risk of thrombotic events. *Id.*[39] Notably, however, data from the group receiving oral Bextra pills only did *not* demonstrate a statistically significant increased risk of thrombotic events compared to the placebo group.[40] Similarly, even when results from the parecoxib / oral Bextra pills group were combined with results from the oral Bextra pills only group – as Furberg did in his editorial – the difference in thrombotic events compared to the placebo group was not statistically significant. *See* Markel Decl., Ex. 87 at 1087 (Nussmeier); *see also* Markel Decl., Ex. 20 at 249 (Furberg et al., CIRCULATION 2005;111:249 [combining those arms in CABG-2 and showing results that were not statistically significant]).[41]

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[39] The CABG-2 study also showed an increased risk of hypotension in the group taking parecoxib, *see* Markel Decl., Ex. 88 at 132, 136, 142-44 (CABG-2 Final Study Report, June 7, 2004 [Tables 20, 21 and 23]), which again is the exact opposite of the increased blood pressure effect that Plaintiffs' experts associate with the use of oral Bextra pills. *See* note 36 *supra*.

[40] *See* Markel Decl., Ex. 87 at 1087 (Nussmeier); *see also* Markel Decl., Ex. 89 at 473, 482 (Mar. 17, 2004 Submission to FDA); Markel Decl., Ex. 83 at 23 (Presentation by Dr. James Witter, Lead Medical Officer at FDA's CDER, Feb. 16, 2005).

[41] At the same time that the parecoxib CABG-2 study was being conducted, the same group of investigators conducted a trial of high-dose, experimental, intravenous parecoxib followed by high-dose oral Bextra pills in patients undergoing non-cardiac surgery. *See* Markel Decl., Ex. 90 at 519 (Nussmeier et al., ANESTHESIOLOGY 2006;104:518-28). That trial, which involved 1062 patients, showed no increased risk of thrombotic events in the group receiving high-dose, experimental, intravenous parecoxib followed by high-dose oral Bextra pills compared to those receiving placebo throughout the study. *See id.* at 523.

4. FDA's Analysis of the Bextra and Intravenous Parecoxib Data

At the Advisory Committee meeting, neither FDA nor the Advisory Committee found any evidence that real-world patients taking Bextra pills for their approved uses are at increased risk of a thrombotic event. Markel Decl., Ex. 23 at 83 (Ad. Comm. Tr., Feb. 17, 2005 [David Graham: "With [Bextra] . . . the information we have at this time suggests that the risk is not increased at doses of 20 mg or less."]); Markel Decl., Ex. 57 at 12 (Ad. Comm. Minutes ["[T]he Committee felt that the evidence was very limited and it is difficult to extrapolate to a real life setting."]). Based on the totality of available cardiovascular data, the Advisory Committee voted to keep Bextra on the market. Markel Decl., Ex. 57 at 11 (Ad. Comm. Minutes).

The Advisory Committee also discussed the high-dose, experimental, intravenous parecoxib CABG trials and concluded – as certain Plaintiffs' experts concede – that the results of those studies – which did not show that patients taking Bextra pills were at increased thrombotic risk – do not establish that the approved use of Bextra increases the risk of heart attack and stroke. *See* Markel Decl., Ex. 23 at 300 (Ad. Comm. Tr., Feb. 18, 2005 [Dr. Shafer: "[I]n the case of cardiopulmonary bypass, I really do think that is a very different kettle of fish."]).[42] Indeed, when Furberg attempted to publish an article using a "meta-analysis" technique to combine data from the Bextra arthritis trials with data from the parecoxib CABG trials, all the journals to which he submitted the article rejected his methodology. *See* Markel Decl., Ex. 7 at 313-14, 320-21 (Furberg Dep., *Haslam v. Pfizer*); *see also* Markel Decl., Ex. 8 at 286 (Furberg Dep. [testifying the CABG results could "probably not" be extrapolated to all patients]).

In FDA's April 6, 2005 decision memorandum, FDA stated that it was "difficult to know how to extrapolate the findings from the parecoxib/[Bextra] CABG trials to the chronic use

[42] *See also* Markel Decl., Ex. 23 at 302-303 (Ad. Comm. Tr., Feb. 18, 2005 [Dr. Abramson: "I don't know how to apply that knowledge to patients that are going to get 10 or 20 milligrams of the drug with arthritis. What I do know is that giving 40 milligrams right after cardiopulmonary bypass is not a good idea."); Markel Decl., Ex. 23 at 530 (Ad. Comm. Tr., Feb. 16, 2005 [Dr. Shafer: "The CABG population is very different, very much a pro-inflammatory population."]); Markel Decl., Ex. 3 at 328-29 (Bennett Dep., *In re Bextra*); Markel Decl., Ex 20 at 249 (Furberg et al., CIRCULATION 2005;111:249 ["It is currently unclear to what degree such risk extends to patients treated chronically with lower doses for arthritis."]).

situation given the significant physiologic and traumatic impact on the coronary vasculature during and following CABG surgery, and the systematic pro-inflammatory response resulting from heart-lung bypass." Markel Decl., Ex. 55 at 9 (FDA Decision Mem.). Significantly, FDA also noted that it is not possible to conclude that Bextra pills are any less safe for the heart than the non-selective NSAIDs on the market, including prescription Motrin and Aleve. *See id.* at 17 (noting that "we have no data showing that Bextra is worse than other NSAIDs with regard to [cardiovascular] risk"). Pending the availability of additional data, *see id.* at 9, FDA nonetheless made a precautionary public health assumption that Bextra, like other NSAIDs, carried an increased thrombotic risk "at least at some dose, with reasonably prolonged use." *Id.* at 10.

However, FDA also stated that its precautionary public health assumption "would not be sufficient to warrant withdrawal of Bextra since we have no data showing that Bextra is worse than other NSAIDs with regard to [cardiovascular] risk." *Id.* at 17. FDA ultimately recommended the withdrawal based on actual data that distinguished Bextra from other NSAIDs on the basis of an increased risk of rare, but severe skin reactions. *Id.* at 17-18. Accordingly, on April 7, 2005, Pfizer voluntarily removed Bextra from the market.

After Pfizer withdrew Bextra, independent researchers continued to evaluate the cardiovascular health of real-world arthritis patients who had taken Bextra pills that were prescribed in real life by their doctors. Well-conducted observational studies – including one co-authored by Dr. Graham of FDA – showed that patients taking Bextra were at no greater risk of a heart attack or stroke than patients taking another NSAID or no NSAID at all. *See* Markel Decl., Ex. 91 at 1382-83 (Solomon D. et al., ARTHR. RHEUM. 2006; 54:1378-89). Similarly, a series of meta-analyses of the Bextra clinical trials that did not include parecoxib – most of which were published after Pfizer withdrew Bextra – found no statistically significant evidence that Bextra increased the risk of heart attack or stroke compared to placebo pills or any other NSAID.[43]

[43] *See* Markel Decl., Ex. 93 at 569 (Chen et al., J. CLIN. PHARM. THER. 2006; 31:565-76); Markel Decl., Ex. 94 at 769 (Chen et al., PHARMACOEPIDEMIOL. DRUG SAF. 2007; 16:762-72); Markel Decl., Ex. 95 at Table S2 (Edwards et

None of these independent researchers employed methodologies that relied on the intravenous parecoxib data to reach conclusions about the cardiovascular safety of Bextra.

ARGUMENT

Rule 702 of the Federal Rules of Evidence imposes certain requirements for the admission of expert testimony:

> If scientific, technical, or other specialized knowledge will assist the trier of fact to understand the evidence or to determine a fact in issue, a witness qualified as an expert by knowledge, skill, experience, training, or education, may testify thereto in the form of an opinion or otherwise, if (1) the testimony is based upon sufficient facts or data, (2) the testimony is the product of reliable principles and methods, and (3) the witness has applied the principles and methods reliably to the facts of the case.

Fed. R. Evid. 702.

In *Daubert*, the United States Supreme Court explained that district courts serve a "gatekeeping" function under Rule 702 to ensure that "any and all scientific testimony or evidence admitted is not only relevant, but reliable." 509 U.S. at 589. The district courts must serve as the gatekeepers of expert testimony because such evidence "'can be both powerful and quite misleading'" to juries. *Id*. at 595 (*quoting* Jack B. Weinstein, *Rule 702 of the Federal Rules of Evidence is Sound; It Should Not Be Amended*, 138 F.R.D. 631, 632 (1991)).

Rule 702 requires that a proposed expert witness possess specialized knowledge, skill, experience, training, or education in the area of his or her proposed testimony. However, even if a proposed expert witness possesses credentials to render certain expert opinions on one subject, the trial court should exclude any testimony that extends beyond the witness's demonstrated expertise. *McCullock v. H.B. Fuller Co.*, 981 F.2d 656, 657-58 (2d Cir. 1992) (holding that an engineer was qualified to testify about the need for ventilation when using a hazardous product, but not regarding the sufficiency of the warning about that risk on the product's label); *Wheeling*

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al., PAIN 2004; 111:286-96); Markel Decl., Ex. 60 at 1305 (Kearney); Markel Decl., Ex. 96 at 248 (White et al., AM. J. THER. 2004; 11:244-50).

Pitt. Steel Corp. v. Beelman River Terminals, Inc., 254 F.3d 706, 715 (8th Cir. 2001) ("Once initial expert qualifications and usefulness to the jury are established, however, a district court must continue to perform its gatekeeping role by ensuring that the actual testimony does not exceed the scope of the expert's expertise, which if not done can render expert testimony unreliable under Rule 702"); *Quintanilla v. Komori Am. Corp.*, No. 07-23475-CV, 2009 WL 320186, at *1 (3d Cir. Feb. 10, 2009) (excluding proposed expert testimony regarding the design of a printing press where the purported expert "ha[d] experience in the mechanical design of certain specific mechanisms . . . [but] there is no indication that [the purported expert's] work involves machines that are in any way similar to printing presses, or that he has received any education or training regarding printing presses or similar machines").

In addition to ensuring that an expert is qualified, the Court must evaluate whether proposed expert testimony has sufficient indicia of reliability, and in doing so must "make certain that an expert . . . employs in the courtroom the same level of intellectual rigor that characterizes the practice of an expert in the relevant field." *Kumho Tire*, 526 U.S. at 152.[44] The reliability of proposed expert testimony is determined by examining "whether the reasoning or methodology underlying the testimony is scientifically valid." *Daubert*, 509 U.S. at 592-93.[45] To be admissible, "it is critical that an expert's analysis be reliable at every step." *Amorgianos v. National R.R. Passenger Corp.*, 303 F.3d 256, 267 (2d Cir. 2002). "In deciding whether a step in an expert's analysis is unreliable, the district court should undertake a rigorous examination of

[44] Under Federal Rule of Evidence 104(a), Plaintiffs bear the burden of proving the admissibility of their proposed experts' testimony. *See Daubert*, 509 U.S. at 592 n.10; Fed. R. Evid. 702 Advisory Comm. Notes (2000 Amend.) (noting that "the admissibility of all expert testimony is governed by the principles of Rule 104(a)").

[45] In *Daubert*, the Supreme Court identified the following considerations as relevant in determining the reliability of proposed expert testimony: (1) whether the expert's technique or theory can be or has been tested – that is, whether the expert's theory can be challenged in some objective sense, or whether it is instead simply a subjective, conclusory approach that cannot reasonably be assessed for reliability; (2) whether the technique or theory has been subject to peer review and publication; (3) whether there are known or potential rates of error with regard to the specific techniques or theories when applied; and (4) whether the theory or approach has "general acceptance" in the relevant scientific community. *Id.* at 590-94.

the facts on which the expert relies, the method by which the expert draws an opinion from those facts, and how the expert applies the facts and methods to the case at hand." *Id.*

The Second Circuit has made clear that "[w]hen an expert opinion is based on data, a methodology, or studies that are simply inadequate to support the conclusions reached, *Daubert* and Rule 702 mandate the exclusion of that unreliable opinion testimony." *Id.* at 266. The district courts in this Circuit consistently have adhered to this mandate by excluding proposed expert testimony that lacks sufficient indicia of reliability. *See Innis Arden Golf Club v. Pitney Bowes, Inc.*, No. 3:06cv1352, 2009 WL 1834244, at *14 (D. Conn. June 26, 2009) (excluding proposed expert testimony under Rule 702 of the Federal Rules of Evidence where "the opinions are neither 'based on sufficient facts or data' nor 'the product of reliable principles and methods'"); *Kass v. West Bend Co.*, No. 02-CV-3719, 2004 WL 2475606, at *10 (E.D.N.Y. Nov. 4, 2004) ("While the plaintiffs contend that any flaws in [the expert's] testimony should go to the weight of the proffered evidence, rather than its admissibility, there is simply too great an analytical gap between [the expert's] unreliable methodology and untested theories and the conclusions he reaches in his report"), *aff'd*, 158 Fed. Appx. 352 (2d Cir. 2005); *Algarin v. New York City Dep't of Corr.*, 460 F. Supp. 2d 469, 476-78 (S.D.N.Y. 2006) (excluding doctor's proposed expert testimony because he "never articulate[d], in any legally cognizable way, what are the standards," and failed to use "any reliable principle or methodology"), *aff'd*, 267 Fed. Appx. 24 (2d Cir. 2008); *Playtex Prods., Inc. v. Procter & Gamble Co.*, No. 02 Civ. 8046, 2003 WL 21242769, at *10 (S.D.N.Y. May 28, 2003) (excluding purported expert's opinions because they were based on no "discernable methodology, have not been subject to peer review and cannot be tested or verified"), *aff'd*, 126 Fed. Appx. 32 (2d Cir. 2005).[46]

[46] As Justice Blackmun explained in *Daubert*, "'[s]cientific methodology today is based on generating hypotheses and testing them to see if they can be falsified; indeed, this methodology is what distinguishes science from other fields of human inquiry.'" 509 U.S. at 593 (*quoting* Michael D. Green, *Expert Witnesses & Sufficiency of Evidence in Toxic Substances Litig.: The Legacy of Agent Orange & Bendectin Litig.*, 86 Nw. U. L. Rev. 643, 645 (1992)).

Significantly, numerous courts have recognized that expert testimony which incorporates only a portion of the available evidence, or "cherry-picks" the data that suits the expert's desired conclusion, is not sufficiently reliable and should be excluded under Rule 702 and *Daubert*. *See In re Rezulin*, 369 F. Supp. 2d at 437 (noting that "courts have excluded expert testimony 'where the expert selectively chose his support from the scientific landscape'") (*quoting Carnegie Mellon Univ. v. Hoffmann-LaRoche, Inc.*, 55 F. Supp. 2d 1024, 1039 (N.D. Cal. 1999), *aff'd*, 541 F.3d 1115 (Fed. Cir. 2008)); *Lust v. Merrell Dow Pharms., Inc.*, 89 F.3d 594, 596 (9th Cir. 1996) (affirming district court's exclusion of proposed expert testimony where the purported expert "'has seen fit to "pick and chose" [sic] from the scientific landscape and present the Court with what he believes the final picture looks like'"); *MTX Commc'ns Corp. v. LDDS/WorldCom, Inc.*, 132 F. Supp. 2d 289, 292 (S.D.N.Y. 2001) (excluding expert's testimony where he failed to consider relevant evidence in formulating his opinions). Rather, in order for expert testimony to be sufficiently reliable to present to the jury, the expert witness must consider the totality of evidence, and "account[] adequately for obvious alternative explanations." *In re Rezulin*, 369 F. Supp. 2d at 425; *see also Carnegie Mellon*, 55 F. Supp. 2d at 1038 (finding purported expert's testimony flawed and unreliable under *Daubert* where the expert "rel[ied] [up]on a single piece of preliminary data and ignores multiple pieces of subsequent contradictory data"); *Miller v. Pfizer, Inc.*, 196 F. Supp. 2d 1062, 1081 (D. Kan. 2002) ("The Court therefore concludes that in failing to discuss the consistency of his hypothesis with other research, Dr. Healy has not used generally accepted methodology"), *aff'd*, 356 F.3d 1326 (10th Cir.), *cert. denied*, 543 U.S. 917 (2004).

In re Rezulin is instructive. In that case, the plaintiffs offered the testimony of a number of purported expert witnesses who opined that the prescription drug Rezulin was capable of causing "silent" liver injury. The defendants moved to exclude such testimony under Rule 702 and *Daubert*. 369 F. Supp. 2d at 402. The court granted the defendants' motion, in part because it found that "the plaintiffs' experts have ignored a large amount of information that calls many aspects of the silent injury theory into question." *Id.* at 425. Specifically, the court stated:

> "In other words, [plaintiffs' experts] have discussed only the evidence that they believed would advance the plaintiffs' position. Their reports cannot be said to reflect 'the same level of intellectual rigor that characterizes the practice of an expert in the relevant field.'"

Id. at 426 (*quoting Kumho Tire*, 526 U.S. at 152). Since the plaintiffs' experts failed to acknowledge or account for "evidence tending to refute [their] theory," *id.* at 425, the court found the proposed testimony unreliable and therefore inadmissible under *Daubert*.[47] *See id.* at 426.

Applying the foregoing principles in this case, the proposed testimony from all of Plaintiffs' experts – that prior to December 16, 2004, there existed reliable scientific evidence that Celebrex and/or Bextra was associated with a statistically significant increase in the risk of heart attacks and strokes – should be excluded under Rule 702 because each of their opinions suffers from some or all of the following flaws:

> Plaintiffs' experts' base their Celebrex and Bextra opinions on data related to other medications (*i.e.*, Vioxx or parecoxib), but have no reliable methodologies to establish that the effects of these other medications are the same as those of Celebrex and Bextra;
>
> Even if Plaintiffs' experts properly confine their analyses to the Celebrex and Bextra data, the experts' few statistically significant claims that remain still are unreliable because they are based on new, cherry-picked composite endpoint definitions, which were intended to fit their desired statistical results, and which have not been used as measures of thrombotic safety in clinical trials or in the peer-reviewed medical literature; and

[47] Likewise, an expert's opinion can be deemed reliable only if it is objective and can be validated. *Daubert*, 509 U.S. at 593; *see also Faryniarz v. Nike, Inc.*, No. 00 Civ. 2623, 2002 WL 1968351, at *2 (S.D.N.Y. Aug. 23, 2002) (same); *In re Accutane Prods. Liab. Litig.*, No. 8:04-md-2523-T-30TBM, 2007 WL 1752593, at *7 (M.D. Fla. June 15, 2007) (holding that a theory which cannot be validated is "not proof of causation" because it "does not show the reliability of each step necessary to make the testimony admissible under *Daubert*"). Thus, where a purported expert witness relies on a theory or hypothesis which is not objective and cannot be validated, courts consistently have excluded such expert's testimony as insufficiently reliable under Rule 702 of the Federal Rules of Evidence and *Daubert*. *See, e.g., Stone v. 866 3rd Next Generation Hotel, LLC*, No. 99 Civ. 4780LTSKNF, 2002 WL 1046706, at *3 (S.D.N.Y. May 22, 2002) (excluding expert report offered by plaintiff under Rule 702 and *Daubert* because there were no means by which to validate the purported expert's hypotheses); *Playtex Prods.*, 2003 WL 21242769, at *10 (same); *In re Rezulin*, 369 F. Supp. 2d at 423 (same).

> Even if certain composite endpoint definitions are valid measures of thrombotic safety, the methods used to collect and classify thrombotic events under those definitions are untrustworthy and unreliable, and never have been used in clinical trials or in the peer-reviewed medical literature.

Statistically significant differences are only as reliable as the information upon which they rest. Here, because Plaintiffs' experts unreliably manipulated the available information to create their statistically significant differences, and because reliable methodologies fail to replicate those differences, any opinions based on those differences should be excluded as a matter of law.

Plaintiffs employ these manipulations to avoid having to reach the conclusions flowing from an appropriate analysis. As FDA, Judge Breyer, and Defendants' experts all observed – and as certain Plaintiffs' experts concede – the only study showing statistically significant differences in the incidence of thrombotic events between patients taking Celebrex and patients taking no medication is the APC trial, which NCI halted on December 16, 2004 and which Pfizer publicly disclosed the next day. The Alzheimer's 001 trial upon which certain Plaintiffs' experts rely, when analyzed according to reliable, conventionally accepted methodologies (including as performed by FDA), did not show statistically significant differences with respect to the risk of thrombotic events such as heart attack and stroke.

Likewise, with respect to the thrombotic safety of Bextra, Plaintiffs' experts rely almost exclusively on the results of CABG-1 and CABG-2, which involved the use of high-dose, intravenous parecoxib followed by high-dose oral Bextra pills in patients who had just undergone open heart bypass surgery. Certain of Plaintiffs' experts concede that the CABG-1 results did not show a statistically significant difference in thrombotic events, and others concede that in the CABG-2 study, the group receiving oral Bextra pills only also did not experience statistically more heart attacks and strokes than patients receiving the standard of care medication for surgical pain relief. In other words, even if an expert considers *not* the totality of evidence – but only the one Celebrex and two Bextra studies that Plaintiffs primarily rely on – and that expert analyzes those studies utilizing accepted methodologies, there would be no

statistical evidence that either Bextra or Celebrex increased the risk of thrombotic events before December 16, 2004.

III. PLAINTIFFS' EXPERTS ARE NOT QUALIFIED AND EMPLOY UNRELIABLE OR NON-EXISTENT METHODOLOGIES, REQUIRING THIS COURT TO EXCLUDE THEIR OPINIONS AND TESTIMONY UNDER RULE 702

A. Madigan's Methodology Is Unreliable And His Opinions Should Be Excluded

Madigan performed a so-called meta-analysis of certain Celebrex trials, and opines based on that analysis that Celebrex is associated with thrombotic risk. He does not offer any opinions relating to Bextra. *See generally* Markel Decl., Ex. 97 (Madigan Rep.). Each part of his analysis – from collection of what he deems to be relevant data to his conclusions based on that data – runs contrary to basic tenets of clinical research as articulated by Plaintiffs' own experts, is riddled with subjective opinions which cannot be validated, and otherwise is so thoroughly unreliable that it must be excluded under Rule 702 and *Daubert*.

1. Madigan Is Not Qualified To Select Cardiovascular Endpoints And He Has Selected An Endpoint That Is Not Clinically Valid

As noted above, Plaintiffs' own experts confirm that a researcher conducting a post hoc analysis, such as the one Madigan performed in this case, must rely on medical doctors in the relevant field (here, cardiologists) to choose a clinically relevant endpoint—before looking at the trials' results—and then apply that endpoint consistently across all the trials being reviewed, rather than changing the endpoint definition from trial to trial depending on the results. Madigan's approach violates these principles and therefore is not reliable.

Madigan uses a different endpoint in this litigation than he used in the Vioxx litigation, even though he maintains that all selective COX-2 inhibitors increase the risk of thrombotic events and share the same mechanism of harm.[48] *See* Markel Decl., Ex. 13 at 237-39 (Madigan

[48] Every one of the Vioxx jury trials involved allegations that Vioxx caused blood clots in the arteries of individual plaintiffs, and not any of the other types of outcomes Plaintiffs mix and match here.

Dep.). In the Vioxx litigation, Madigan used a composite endpoint that focused on thrombotic events – *including stroke* – to evaluate the cardiovascular safety of Vioxx.[49]

Here, however, Madigan abandons his Vioxx litigation methodology, including use of the well-accepted APTC endpoint, because use of that endpoint does not yield the results that Plaintiffs need to sustain a case against Celebrex. *See* App., Fig. 1 (listing Madigan's departures from his Vioxx methodology). Instead, he chose to invent what he calls the "Hard CHD" endpoint, in which he includes heart attacks and sudden cardiac death, *but not stroke*. *See* Markel Decl., Ex. 13 at 89, 229-31 (Madigan Dep.).

Madigan plainly is not qualified to select an endpoint for assessing thrombotic risk on his own. He does not have a medical degree, he has no formal education or training in toxicology, pharmacology or biochemistry, and he does not hold himself out as an expert in any of those fields. *See* Markel Decl., Ex., 99 at 10-11 (Madigan Dep., *Grutka v. Pfizer*). Madigan does not know the definition of various cardiovascular events, despite using the terms in his report. See Markel Decl., Ex. 13 at 247 (Madigan Dep.). For example, he does not know what a fatal coronary heart disease ("CHD") event is or whether a sudden cardiac death can be classified as a fatal CHD event. *Id.* at 247-49.[50]

Madigan also admits that he has no prior experience with his so-called "Hard CHD" endpoint. *See id.* at 245. He acknowledges that neither his invented "Hard CHD" endpoint – nor any of the other endpoints he uses in his report[51] – was ever used in the peer-reviewed literature to analyze the safety of COX-2 inhibitors prior to December 2004. Markel Decl., Ex. 13 at 230, 255-57 (Madigan Dep.); *see also* Markel Decl., Ex. 60 (Kearney [meta-analysis of clinical trials

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[49] *See* Markel Decl., Ex. 99 at 85-86 (Madigan Dep., *Grutka v. Pfizer*); Markel Decl., Ex. 100 at 14, 33-35 (Madigan Vioxx Rep.) *see also id.* at 2 (noting that "a complete characterization of Vioxx's cardiovascular risk profile should include an array of thrombotic events, not just MI").

[50] Madigan claims that he selected the "Hard CHD" endpoint because it is what Plaintiffs' expert Kronmal used in the Vioxx litigation, *see id.* at 237, 239-40, but Kronmal does not use the "Hard CHD" endpoint here and instead advocates the use of yet another endpoint: heart attacks alone. *See* Markel Decl., Ex. 12 at 121-22 (Kronmal Dep.).

[51] Madigan also uses a myocardial thromboembolic endpoint, a serious cardiovascular thrombotic endpoint, and a cardiovascular mortality endpoint. Markel Decl., Ex. 97 at 4-5 (Madigan Rep.).

using APTC endpoint]); Markel Decl., Ex. 55 (FDA Decision Mem. [analyzing APTC endpoint]). Further, the article Madigan cites to support his brand new endpoint did not use that measure at all. *Compare* Markel Decl., Ex. 101 (Sever et al., LANCET 2003;361:1149-1158 [evaluating heart attacks and fatal coronary heart disease]) *with* Markel Decl., Ex. 97 at 4 (Madigan Rep. [evaluating heart attacks and sudden cardiac death]). Even worse, Madigan does not understand his newly fabricated endpoint. He included "cardiac thrombus" in his "Hard CHD" endpoint, but he admitted he had no idea what that term means. *See* Markel Decl., Ex. 13 at 247 (Madigan Dep.). He also could not define a fatal CHD event. *See id.* at 247-48.[52]

While Madigan claims he consulted with Baruch – Plaintiffs' only cardiologist – to validate that the "Hard CHD" endpoint was appropriate, Baruch could recall doing no such thing. *See* Markel Decl., Ex. 161 at 41-43 (Baruch Dep.). At his deposition, Baruch was not familiar with the "Hard CHD" endpoint, could not define it, and could not recall ever using that endpoint himself or even reading a published paper that used it. *See id.* at 43-44, 46-48. In fact, Baruch testified that the endpoints in which he is predominantly interested as a cardiologist are heart attack, stroke, and cardiovascular death – that is, the APTC endpoint. *See id.* at 147. Baruch also noted that combining sudden cardiac death with non-fatal heart attacks is imprecise in that many sudden cardiac deaths may not be caused by coronary heart disease. *See id.* at 100-01 (agreeing that all sudden cardiac deaths are not necessarily "CHD deaths"); *id.* at 117-19 (noting it is inappropriate "as a blanket" to combine sudden cardiac deaths with non-fatal heart attacks).[53]

In short, Madigan's analysis constitutes a variation on the cherry-picking engaged in by

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[52] Madigan admits he knows just as little about the outcomes that he includes in his other composite endpoints. Asked whether he was aware of any theoretical support linking Celebrex or COX-2 inhibitors to many of the events included in these composite endpoints, Madigan admitted, "No, I'm not," and further admitted that he does not know what many of the terms mean. *See, e.g., id.* at 187-91 (Madigan Dep. [cardiac arrest ("I don't know"), sudden death ("I don't know"), cardiac thrombus ("I don't know")]).

[53] Sudden cardiac death ("SCD") is death resulting from an abrupt loss of heart function and is broader than fatal coronary heart disease, which is just one possible cause of SCD. *See* American Heart Ass'n, *Sudden Cardiac Death, available at* http://www.americanheart.org/presenter.jhtml?identifier=4741 (last visited July 16, 2009).

all of Plaintiffs'' experts: he abandoned the endpoint he had used previously and which Plaintiffs' other experts have endorsed outside of this litigation and instead chose one (when he was not qualified to do so) in order to reach a conclusion preferred by Plaintiffs. Such a "methodology" plainly lacks "the same level of intellectual rigor that characterizes the practice of an expert in the relevant field," *Kumho Tire*, 526 U.S. at 152, and therefore, Madigan's testimony is inadmissible.

2. Madigan's Unreliable Data Collection

The Second Circuit has cautioned that to be admissible, "it is critical that an expert's analysis be reliable at every step." *Amorgianos*, 303 F.3d at 267. An essential aspect of Madigan's approach involved the collection of the data upon which his analysis rests. As previously noted, particularly in the case of a post-hoc analysis such as Madigan's, qualified medical doctors must collect data relevant to the endpoint in a way that is reliable and consistent, such as by gathering complete and accurate information about the adverse events that fulfill the chosen endpoint definition from published medical journal articles, study reports filed with FDA, and electronic (or SAS) data files containing certain patient level data. Contrary to accepted practices, Madigan's data collection efforts here are undocumented and slipshod.

Madigan relied entirely on information from electronic SAS data files, with no review of actual patient information from study reports or published articles. *See* Markel Decl., Ex. 13 at 99-100 (Madigan Dep.). Further, Madigan did not review any study reports to inform his opinions and ensure that he had captured all relevant patient medical outcomes related to his endpoint. *Id.* at 100, 253. He also concedes that all of the events in the SAS data files were unadjudicated events. *Id.* at 101.

Because Madigan did not review study reports, he did not count events himself and instead wrote a computer program to search for certain terms that he would count in his endpoints. *See id.* at 96-100. Madigan testified that he relied on Baruch to select the appropriate terms for his endpoints, particularly the "Hard CHD" endpoint. *Id.* at 52-55, 195. Yet Baruch

testified that he had no recollection of selecting those terms. Markel Decl., Ex. 161 at 38-41 (Baruch Dep.). Similarly, Baruch could not provide critical details about the origin of the terms he reviewed with Madigan, testifying that some of the terms were derived from regulatory medical dictionaries, while others originated from other sources with which he was not familiar. *Id.* at 21. Baruch does not recall how he obtained the dictionary that he used, what version of the dictionary he used, or what level of terms were used. *Id.* at 57-58. Baruch also could not remember whether he discussed the terms with Madigan or gave him any advice about the appropriateness of the three endpoints that Madigan chose. *Id.* at 41-43. Thus, Baruch admittedly could offer no proof that the list of terms Madigan used to search for "Hard CHD" or his other endpoints were valid ones to use. *Id.* at 163-65.

Madigan's failure to collect data in a thorough, reliable way infects his results. Madigan counted only nine cardiovascular deaths in his analysis of pre-2004 Celebrex trials. *See* Markel Decl., Ex. 97 at 34 (Madigan Rep.). By relying solely on the SAS data files, rather than the actual source of medical information pertaining to individual patients, Madigan missed two cardiovascular deaths, both of which occurred in patients taking placebo. Markel Decl., Ex. 161 at 134-36 (Baruch Dep. [reviewing events in study reports that were not in the electronic data files]). He also missed two cardiovascular deaths that were reported both in the SAS data file and in the study report, which he might have realized had he checked his event counts against the source. *Id.* at 140-42 (same). Had Madigan included those four deaths, his analysis would not have yielded statistically significant results, even at the highest Celebrex doses.

3. Madigan's Unreliable Data Classification

After fabricating a novel endpoint and collecting event data based on undefined, undocumented terms, which missed a material number of events that would have changed his results, Madigan then had to classify the events produced by the undocumented and unvalidated computer search. To account for inconsistencies in the criteria used to diagnose medical outcomes across the various trials and make sure that no events were missed or misclassified,

however, Madigan needed to establish rules for how patients' medical outcomes were collected and classified across the entire dataset.

Indeed, like Plaintiffs' other experts, Madigan acknowledges that the classification of events is a "very important" part of his analysis, that blinded adjudication can reduce misclassification of events, and that an inappropriately classified event could invalidate his results.[54] *See* Markel Decl., Ex. 13 at 60, 63-64 (Madigan Dep.). Madigan even admits that he prefers to work with adjudicated data because it increases the reliability of the classifications he uses. *See id.* at 64-65. Yet Madigan did not adjudicate any events because he lacks the necessary cardiology background to do so. *See id.* at 100-01. He thus proceeded to rely not just on an unwritten, unblinded classification of events by the cardiologist Baruch, but on a post hoc, undisclosed, unwritten, unblinded *reclassification* of a select group of those events by the unlicensed, non-cardiologist Furberg.

Baruch's Unwritten, Unblinded Classification of Events. Baruch originally classified certain cardiovascular events for Madigan in connection with a prior personal injury suit involving Celebrex. Markel Decl., Ex. 161 at 11, 14, 17, 37-38, 71-72 (Baruch Dep.); Markel Decl., Ex. 13 at 44-45, 58-59, 65-66 (Madigan Dep.). At that time, Baruch reviewed several spreadsheets listing the relevant trials, patient identification numbers, and a "phrase or a word" describing the patients' events. Markel Decl., Ex. 161 at 17-18, 21 (Baruch Dep.). To his recollection, Baruch categorized the various events for Madigan based solely on that information; Baruch does not recall whether he had any medical records or other original sources of patient information at his disposal during the review. *Id.* at 20-21.

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[54] Baruch, Furberg, and Kronmal agree. *See, e.g.*, Markel Decl., Ex. 161 at 80-82, 96-97 (Baruch Dep. [agreeing that adjudication committees ordinarily have pre-specified criteria to define events, that adjudications should be blinded so that the medical doctor evaluating the events does not know whether the patient at issue was taking the study medication or a comparator agent, and that it is important to understand the criteria used by an adjudication in order to determine whether the adjudication process is valid]); Markel Decl., Ex. 12 at 129, 230-31 (Kronmal Dep. [testifying that adjudication committees operate by predetermined rules that are applied to classify events uniformly and doctors usually adjudicate events without knowing the medication the patient is taking]); Markel Decl., Ex. 7 at 770 (Furberg Dep., *Haslam v. Pfizer* [stating that adjudications typically are done by committee to avoid subjectivity]).

Yet just as Baruch could not recall validating Madigan's "Hard CHD" endpoint or helping him select search terms for collecting events in the SAS data files, Baruch testified that he had no recollection of the criteria that he applied in evaluating the death events for Madigan's analysis. *Id.* at 77-79, 128, 131. In fact, Baruch admits that the entire classification process, including the criteria used to classify events and any evidence that he applied those criteria correctly to the events at issue, is undocumented. *Id.* at 163-65.

In light of these deficiencies, and Baruch's lack of experience with adjudication, *see id.* at 80 (admitting that he never has served on an adjudication committee for any clinical trial), Baruch was careful to distinguish what he did from a formal adjudication. He claimed that he merely performed a "classification" procedure, and he confirmed that he followed none of the formalities of an actual adjudication process. *Id.* at 71-72 (citing Madigan Dep. at 253-54). As a result, Baruch admitted that he could offer no objective proof that the criteria he applied were appropriate, that he applied those criteria faithfully to each event extracted by Madigan, or that the ultimate result was accurate. *Id.* at 163-65. In fact, Baruch testified that the spreadsheet Plaintiffs' counsel produced as evidence of his classification work was not his and did not reflect his analysis. *Id.* at 74-76. Tellingly, when restricted to data available prior to December 2004 (*i.e.*, eliminating the APC and PreSAP trials), Baruch's original classifications do not show a statistically significant increase in thrombotic risk for patients taking Celebrex compared to those taking placebo, regardless of which of Madigan's various endpoints Baruch reviewed, even when restricted to the highest Celebrex doses. *See* App., Fig. 2.

Furberg's Post Hoc, Undisclosed, Unwritten, Unblinded Reclassification of a Select Group of Events. Apparently dissatisfied with the results of Baruch's original classifications, *Plaintiffs' counsel* (not Madigan) asked Furberg, who is not a cardiologist and has not practiced medicine for more than 30 years, to reclassify certain events analyzed by Baruch – Plaintiffs' only cardiologist. *See* Markel Decl., Ex. 13 at 44-45, 65-67 (Madigan Dep.). During his initial deposition in this case, Furberg denied making any efforts to adjudicate events or to review any patient information from the Celebrex clinical trials. *See* Markel Decl., Ex. 8 at 17-19 (Furberg

Dep. ["No. I don't see that as my role."]). Moreover, in prior testimony, Furberg has criticized attempts to reclassify events in a post hoc way. *See* Markel Decl., Ex. 72 at 58-59 (Furberg Dep., *In re Rezulin* ["Clearly here is an area where they violated the scientific principles. Post hoc they sat down and threw out cases, in violation of basis principles of research"]). It was not until Madigan's deposition that it was revealed for the first time that Furberg *reclassified* a select group of the events originally classified by Baruch. *See* Markel Decl., Ex. 13 at 44-45, 65-67 (Madigan Dep.).[55]

Madigan testified that Furberg's reclassification was not based upon underlying patient medical records, patient narratives in study reports, or other similarly detailed information, but upon a single-line description of the patient's event contained in the spreadsheet Madigan had prepared from the SAS data files. *Id.* at 46-49 (admitting no other information was provided to Furberg through Plaintiffs' lawyers other than the spreadsheet). Furberg testified that it was a challenge to classify events based solely on these single-line descriptions, that he wished he had been given more information, and that he cannot recall ever performing a classification based on such limited data. *See* Markel Decl., Ex. 8 at 343-44, 346, 365-66, 385-86, 402-03, 409 (Furberg Dep.). When asked why he did not perform a proper adjudication based on actual patient records, Furberg testified that "there was no time. There was a deadline, and I would not have the time to do that." *Id.* at 344 (noting that Plaintiffs' counsel asked him to review the spreadsheet over a weekend in early March days before Madigan's report was due, during which time he was "terribly busy").

Moreover, there was no direct contact or communication between Madigan and Furberg about these reclassifications or the basis for them, and there were no written, pre-specified rules about how Furberg (who does not know the criteria for diagnosis of a heart attack) would conduct the reclassification – just a spreadsheet showing the reclassifications themselves.

[55] After learning of Furberg's reclassification, Pfizer requested a further deposition of Furberg to discuss the process by which Furberg reclassified certain events. That deposition took place on July 11, 2009.

Markel Decl., Ex. 13 at 44-50, 66 (Madigan Dep. [admitting Plaintiffs' counsel asked Furberg "to redo that exercise" of classifying a select group of adverse events]). Further, Furberg's reclassifications were performed in an unblinded and non-scientific way with the participation of Plaintiffs' attorneys. *Id.* at 49-50, 66; Markel Decl., Ex. 8 at 365, 384-85, 389 (Furberg Dep.). Even though Madigan testified that he was not dissatisfied with Baruch's original efforts, Madigan used the selective events reclassified by Furberg in his analysis for this litigation. Markel Decl., Ex. 13 at 44-46, 61 (Madigan Dep.). Furberg himself testified that it was improper methodologically for Madigan to rely simply on Furberg's classification and disregard Baruch's previous classification; he agreed that there should have been some defined process whereby Madigan resolved the differences between the two classifications. Markel Decl., Ex. 8 at 388-91 (Furberg Dep.).

Notably, all of Furberg's reclassifications resulted in changes to adverse event counts that weighed against Celebrex. For instance, Furberg's reclassification added six "Hard CHD" events to the Celebrex group and only two to the placebo group. Madigan then inexplicably ignored one of the additional placebo events, resulting in a net increase of five events against Celebrex. *Compare* Markel Decl., Ex. 98 at 8 (Madigan Rep., *Grutka v. Pfize*r [showing 47 "Hard CHD" Celebrex events]) *with* Markel Decl., Ex. 97 at 9 (Madigan Rep. [showing 52 "Hard CHD" Celebrex events]); *see also* Markel Decl., Ex. 13 at 213-14 (Madigan Dep.). For the Alzheimer's 001 trial, Furberg's reclassification added three "Hard CHD" events to the Celebrex group and no such events to the placebo group. *Compare* Markel Decl., Ex. 98 at 8 (Madigan Rep., *Grutka v. Pfizer* [showing two Celebrex events to zero placebo events]) *with* Markel Decl., Ex. 97 at 9 (Madigan Rep. [showing five Celebrex events to zero placebo events]). Furberg's reclassification also added events to the Celebrex groups in the analysis of Madigan's other endpoints, including myocardial thromboembolic events and cardiovascular thromboembolic events. *Compare* Markel Decl., Ex. 98 at 13, 15 (Madigan Rep., *Grutka v.*

Pfizer) *with* Markel Decl., Ex. 97 at 16, 18 (Madigan Rep.); *see also* Markel Decl., Ex. 13 at 215 (Madigan Dep.).[56] Furberg's reclassification did not just increase the number of Celebrex events when compared to Baruch's original classification; his reclassification also increased the number of cardiovascular deaths in the APC and PreSAP trials when compared to the pre-specified, written, blinded adjudication performed by the NIH investigators. *Compare* Markel Decl., Ex. 97 at 32, 34 (Madigan Rep.) *with* Markel Decl., Ex. 134 at 1031 (Solomon et al., CIRCULATION 2006;114:1028-35). Despite these discrepancies, Madigan never compared Baruch's classification to Furberg's reclassification. Markel Decl., Ex. 13 at 67 (Madigan Dep.).

Solely as a result of Furberg's post hoc, undisclosed, unwritten, unblinded reclassification, Madigan's analysis of "Hard CHD events" reached statistical significance, whereas Baruch's original classification did not. *See id.* at 175-76 (admitting that Furberg's reclassification increased the number of Hard CHD events for the Alzheimer's 001 trial from two to five in Table 3 of his report); *see also* App., Fig. 2. Yet, when shown the spreadsheet and asked which of the Alzheimer's 001 patients suffered a "Hard CHD" event (*i.e.*, a myocardial infarction or sudden cardiac death), Furberg identified only one myocardial infarction and one possible sudden cardiac death. Markel Decl., Ex. 8 at 408-09 (Furberg Dep. [calling the sudden cardiac death a "tricky one" where he would need to know more]). In other words, his testimony at deposition – based on the same spreadsheet he reviewed for Plaintiffs' counsel – was inconsistent with the event counts attributed to Furberg in Madigan's report. *Compare id.* at 406-09 *with* Markel Decl., Ex. 97 at 9, 11, 13 (Madigan Rep.). Further, while Plaintiffs have produced a typed spreadsheet that they claim reflects Furberg's reclassification, Furberg himself could not authenticate that document as his or say that it accurately reflected his event counts.

[56] With regard to these endpoints, Furberg testified that he disregarded the pre-specified definitions that he had been given by Madigan and applied his own definitions, even though he never told Madigan or Plaintiffs' counsel that he was applying different definitions than the ones that he had been given. Markel Decl., Ex. 8 at 396-400, 435 (Furberg Dep. [admitting Madigan "probably didn't know" that Furberg was applying different definitions]; *id.* at 435 [acknowledging that Madigan should have been told which definitions Furberg was applying: "If he reports on it, he needs to know how the data were classified."]).

Markel Decl., Ex. 8 at 385, 393 (Furberg Dep.); *see also* Markel Decl., Ex. 161 at 74 (Baruch Dep. [testifying similarly that the spreadsheet Plaintiffs attribute to him was not his]). Notably, even accepting all of these methodological problems, when limited to trials completed prior to December 2004 (*i.e.*, eliminating APC and PreSAP), Madigan's reclassified "Hard CHD" endpoint achieves statistical significance only at the highest Celebrex doses. *See* App., Fig. 2.

The icing on the cake came after Madigan's deposition. After Madigan testified under oath that it was only with Furberg's reclassification that his analysis was able to demonstrate a statistically significant increase in the risk of "Hard CHD" events, *Plaintiffs' counsel* – not Madigan himself – attempted to claim that Madigan's original analysis was erroneous. *See* Markel Decl., Ex. 103 at 2 (Ltr. from Geoffrey C. Jarvis, July 6, 2009).

Perhaps aware of the impermissible nature of their post hoc, unwritten, unblinded reclassification, Madigan, Baruch and Furberg appear to have made an effort to hide the existence of these classification procedures. According to Madigan, his failure to disclose Furberg's role in reclassifying the events described in his report was an oversight, albeit one he repeated in failing to disclose similar classifications by others in a previous Celebrex report. *See* Markel Decl., Ex. 13 at 58-59 (Madigan Dep. [acknowledging failure to report Baruch's assistance with his report in the Grutka case, the same as his failure to disclose Furberg's classifications here]). He further acknowledged that, despite these repeated oversights, this reclassification process that Furberg conducted was an important part of Madigan's analysis in this litigation. *Id.* at 44-45, 58-60. Similarly, when asked during his deposition whether he had adjudicated any events, Furberg denied any involvement and testified that he did not adjudicate any events in the Celebrex clinical trial database. Markel Decl., Ex. 8 at 18-19 (Furberg Dep.).

As should be clear from the foregoing, Madigan's event classification, which he and all Plaintiffs' other experts acknowledge is crucial to Madigan's analysis, lacks any indicia of reliability. While the Second Circuit mandates that "each step" of an expert's analysis be reliable in order for the opinion to be admissible, *Amorgianos*, 303 F.3d at 267, this essential element of Madigan's "methodology" never was documented, was undertaken by Madigan in a

haphazard fashion that is the antithesis of a consistent, principled approach, and, once Furberg's reclassification is considered, was plainly calculated to reach a predetermined result favored by Plaintiffs' counsel. Opinions based on such fundamentally and pervasively flawed methods of data collection must be excluded. *Playtex Prods.*, 2003 WL 21242769, at *10 (excluding expert opinions which are based on no "discernable methodology, have not been subject to peer review and cannot be tested or verified").

B. Furberg's Opinions Are Unreliable And Therefore Inadmissible

Curt Furberg, an administrator at Wake Forest University who is neither a cardiologist, a practicing medical doctor nor an expert in statistics, is Plaintiffs' so-called "drug safety" expert. *See* Markel Decl., Ex. 1 at 37 (Furberg Rep.); Markel Decl., Ex. 8 at 173, 246 (Furberg Dep.). Furberg never has been licensed to practice medicine in the U.S., has not prescribed a medication in more than thirty-five years, and admits that he is not competent to practice medicine today. Markel Decl., Ex. 104 at 49 (Furberg Baycol Dep.). Furberg is not a cardiologist, does not know the criteria for diagnosing a heart attack, and cannot and does not diagnose cardiovascular conditions in patients. *See id.* at 44-45; Markel Decl., Ex. 8 at 183 (Furberg Dep. ["I can't give you the criteria without you giving me the guidelines from the American Heart Association."]); *id.* at 151; *see also* Markel Decl., Ex. 105 at 20 (Furberg Dep., *Sturgill v. Johnson & Johnson Co.*).

In this action, Furberg claims to have reviewed certain select clinical trials involving high-dose administration of Celebrex or parecoxib and opines, based on that review, that Celebrex and Bextra are associated with thrombotic risk. Because his analysis is replete with methodological flaws, including that it is devoid of any pre-specified, objective criteria for determining an association between Celebrex or Bextra and thrombotic risk, the Court should exclude his proposed testimony. *Daubert*, 509 U.S. at 592-93 (proposed expert testimony should be excluded as unreliable where it cannot be demonstrated that the reasoning or methodology underlying the testimony is scientifically valid).

1. Furberg's History Of Offering Biased, Methodologically Unsound Opinions To Advance His Agenda Against The Pharmaceutical Industry Generally And Selective COX-2 Inhibitors In Particular

Before discussing the sham process undertaken by Furberg in this case, it is worth observing that his use of flawed methods here to reach a desired conclusion is nothing new. In the last fifteen years, his methods routinely have been criticized and rejected by the medical and scientific communities, others in the clinical research field rarely, if ever, have confirmed his work in subsequent studies, and neither FDA nor medical texts have adopted his drug safety positions. *See* App., Fig. 3.[57] As a litigation expert, Furberg repeatedly has testified against the pharmaceutical industry, including in litigation involving Baycol, Bextra, Fosamax, Neurontin, Omniscan, Ortho-Evra, Propulsid, and Rezulin.[58] In one case, this Court excluded Furberg from testifying about certain subjects, finding that Furberg's position "'is not an "expert" opinion, but rather a personal opinion about what standards [he] believes should apply to pharmaceutical company conduct.'" *In re Rezulin Prods. Liab. Litig.*, 309 F. Supp. 2d 531, 560 (S.D.N.Y. 2004) (citation omitted); *see also id.* at 543 n.32 (noting that judges should not be "'deceived by the assertions of experts who offer credentials rather than analysis'") (citation omitted).

Furberg also came to this litigation with a pre-existing bias against Bextra and Celebrex. In 2004, FDA removed Furberg from the Advisory Committee because of his public comments regarding Bextra. Markel Decl., Ex. 7 at 309-13 (Furberg Dep., *Haslam v. Pfizer*); Markel Decl.,

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[57] *See, e.g.*, Markel Decl., Ex. 106 at B1 (Andrew Pollack, *The Minimal Impact of a Big Hypertension Study*, N.Y. TIMES, Nov. 28, 2008 ["There was a feeling there was a political and economic agenda as much as a scientific agenda. . . . They pushed beyond what the data allowed them to say."]); Markel Decl., Ex. 107 at 2 (Zosia Chustecka, *Experts Condemn Furberg's Meta-Analysis Showing Calcium Channel Blockers to be Inferior*, HEART*WIRE*, Sept. 1, 2000 ["[T]here is no scientific basis for Furberg's conclusions . . . [and] no serious clinical academic in the field agrees with his conclusions."]); Markel Decl., Ex. 108, at B21 (Ridgely Ochs, *A High-Tension Drug Study / Channel Blocker Research Prompts Clash Between Company, Scientists*, NEWSDAY (NY), Oct. 22, 1996); Markel Decl., Ex. 109 (Kaplan, LANCET 1996;348:541-42 [Ltr. to the Editor] ["The[] investigation[] disobey[s] virtually all of the principles of proper observational (case-control or cohort) studies."]); Markel Decl., Ex. 110 at 1 (*Calcium Channel Blocker Debate Continues*, MARKETLETTER, Sept. 11, 1995 ["[I]f one tries to think of all the things to do wrong in a meta-analysis, this paper would have all of them."]).

[58] *See generally* Markel Decl., Ex. 112 (Furberg Rep., Baycol Litigation); Markel Decl., Ex. 7 (Furberg Dep., *Haslam v. Pfizer*); Markel Decl., Ex. 113 (Furberg Rep., *In re Neurontin*); Markel Decl., Ex. 111 (Furberg Rep., *In re Gandolinium*); Markel Decl., Ex. 105 (Furberg Dep., *Sturgill*); Markel Decl., Ex. 114 (Furberg Rep., *In re Rezulin*); *see also* Markel Decl., Ex. 8 at 321-22 (Furberg Dep.).

Ex. 115 at 1 (Gardiner Harris, *New Study Links Pfizer's Bextra, Similar to Vioxx, to Heart Attacks*, N.Y. TIMES, Nov. 10, 2004).[59] Also, before the Advisory Committee meeting, Furberg (along with Garret FitzGerald and Bruce Psaty) wrote an editorial wherein he performed a so-called meta-analysis related to the thrombotic safety of Bextra and parecoxib, which allegedly showed that the medications significantly increased the risk of serious thrombotic events. Markel Decl., Ex. 20 at 249 (Furberg et al., CIRCULATION 2005; 111:249); Markel Decl., Ex. 7 at 179-81 (Furberg Dep., *Haslam v. Pfizer*). The journals LANCET and CIRCULATION both rejected their first iteration of the meta-analysis because Furberg attempted to combine data from Bextra arthritis trials with data from the parecoxib CABG surgery trials. Markel Decl., Ex. 7 at 313-14, 320 (Furberg Dep., *Haslam v. Pfizer*). At the Advisory Committee meeting, and again after the meeting, Furberg criticized Pfizer's written submissions to FDA, but FDA took no further action despite repeated follow-up by Furberg.[60] Furberg later said he felt "vindicated" when Pfizer voluntarily withdrew Bextra.[61]

2. Furberg's Unreliable Celebrex Analysis Should Be Excluded

Consistent with Furberg's pattern of using the ends to justify the means – *i.e.*, employing any analysis that will allow him to reach a predetermined conclusion – his methodology here violates scientific principles as well as almost all principles he has espoused in accepted literature outside of litigation.

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[59] FDA later re-invited Dr. Furberg to participate in the hearing because federal conflict of interest guidelines do not allow for dismissal based on "intellectual bias." Markel Decl., Ex. 116 at A1 (Ricardo Alonso-Zaldivar, *FDA to Institute Safety Board*, L.A. TIMES, Feb. 16, 2005); *see also* Markel Decl., Ex. 117 at 8D (Rita Rubin, *Painkillers Hang in the Balance*, USA TODAY, Feb. 10, 2005); Markel Decl., Ex. 118 at 2 (E.J. Mundell, *Bextra Data Suggests All Cox-2 Drugs Pose Heart Risks*, HEALTH DAY, Jan. 18, 2005); Markel Decl., Ex. 119 at B5 (Diedtra Henderson, *Calls Are Mounting for Revamp of FDA*, BOSTON GLOBE, Dec. 25, 2004).

[60] *See* Markel Decl., Ex. 23 at 340, 478-80 (Ad. Comm. Tr., Feb. 16, 2005); Markel Decl., Ex. 120 (Fax from Paul Z. Balcer, Regulatory Health Project Manager to Pfizer, March 3, 2005); Markel Decl., Ex. 121 (Letter from Curt Furberg to Brian Harvey, Acting Director of CDER's Division of Anti-Inflammatory, Analgesic, and Ophthalmic Drug Products, June 17, 2005); Markel Decl., Ex. 121 (Email from Curt Furberg to Brian Harvey, Aug. 17, 2005); Markel Decl., Ex. 122 (Letter from Curt Furberg to Bob Rappaport, Director of CDER's Division of Anti-Inflammatory, Analgesic, and Ophthalmic Drug Products, Sept. 27, 2005).

[61] *See* Markel Decl., Ex. 7 at 383, 404 (Furberg *Haslam* Dep.); Markel Decl., Ex. 123 at 1A (Rita Rubin, *Another Drug for Pain off Market; Risk vs. Benefit for Bextra Cited*, USA TODAY, Apr., 8, 2005).

a. Furberg's Failure to Use Consistent, Clinically Valid Endpoints

Plaintiffs' experts, including Furberg, agree that a researcher conducting a post hoc analysis should select an endpoint accepted by medical experts in the field of interest and apply that endpoint consistently across all of the trials being reviewed. *See* Section I.C.2 *supra*. When asked about using composite endpoints in post hoc analyses, Furberg emphasized that a researcher should follow a systematic, pre-specified approach and not allow the known results to drive the process: "I think anything that you decide to do that is influenced by the data is suspect." Markel Decl., Ex. 8 at 90-91 (Furberg Dep.); *id.* at 80 ("Post hoc, I don't like any [composite endpoints]. . . . We should not rely on that."). Outside of litigation, Furberg also has warned against post hoc interpretations of clinical trials, noting that "[r]ed flags may include the use of unusual or illogical composites, *e.g.*, outcome measures that have uncertain clinical relevance." Markel Decl., Ex. 5 at 42 (EVALUATING CLINICAL RESEARCH). Systematically applying a clinically valid endpoint prevents an unscrupulous researcher from constructing a composite endpoint from disparate outcomes to create the appearance of a statistically significant difference in events.

Furberg violates his own articulated principles by using several different endpoint definitions across the Celebrex data, choosing whatever combination of events or definition helps contrive a statistically significant difference. *See* Markel Decl., Ex. 8 at 175-76 (Furberg Dep.); Markel Decl., Ex. 1 at 25 (Furberg Rep. [looking only at heart attacks in SUCCESS[62]]); *id.* (looking at heart attack and stroke in APC); *id.* at 26 (looking at adjudicated "serious cardiovascular events" in PreSAP).

For instance, Plaintiffs' experts concede that Alzheimer's 001 is the only Celebrex clinical trial that preceded APC and allegedly showed a statistically significant result. This small

[62] SUCCESS, which involved 13,274 patients, compared those taking 200 mg or 400 mg daily of Celebrex for three months to those taking the non-selective NSAIDs naproxen (Aleve) and diclofenac and found no statistically significant evidence of increased risk of thrombotic events. Markel Decl., Ex. 92 at 255, 264 (Singh et al., AM. J. MED. 2006;119:255-66).

trial involved a sick and elderly patient population and compared a group taking two times the recommended daily doses of Celebrex for one year to a group taking placebo in an experimental study to test whether Celebrex could be effective in treating Alzheimer's patients. In his analysis of this trial, Furberg makes up a composite endpoint of six different outcomes never used before in a clinical study, including atrial fibrillation, a common rhythm disturbance, and several other types of events that are not induced by clots. *See* Markel Decl., Ex. 1 at 18 (Furberg Rep.); Markel Decl., Ex. 8 at 148 (Furberg Dep. [admitting that the composite endpoint that he used in the Alzheimer's 001 trial represents a "wide net" and is "basically the cardiovascular events that were reported"]). Furberg has never before combined all of these outcomes in one endpoint. *See* Markel Decl., Ex. 8 at 154 (Furberg Dep.). In fact, there is no evidence that such an endpoint ever has been used in a clinical trial or by researchers in the medical literature.

Moreover, Furberg's Alzheimer's 001 endpoint conflicts with Plaintiffs' "imbalance" hypothesis.[63] In 1999, when the Alzheimer's 001 trial was completed, Furberg agreed that the relevant public health question – whether NSAIDs increase the risk of thrombotic events – was based on the "imbalance" hypothesis that such medications promote clotting events like heart attack and stroke. *See id.* at 36-38. Yet Furberg admits that rhythm disturbances included among his endpoints, such as atrial fibrillation, are not caused by clotting. *See id.* at 223. That is why Furberg did not include rhythm disturbances in his published editorials outside of litigation,

[63] In his report, Furberg opines that all selective COX-2 inhibitors have a "class effect" of increasing thrombotic risk, and that this class effect was established prior to December 2004. Markel Decl., Ex. 1 at 9-10 (Furberg Rep.). Not only is his selection of endpoints inconsistent with a "class effect," but Furberg concedes that he does not have expertise regarding thrombosis or Plaintiffs' "imbalance" hypothesis, which is the biological basis of Plaintiffs' claims. Markel Decl., Ex. 8 at 24-25 (Furberg Dep.); Markel Decl., Ex. 7 at 20-21 (Furberg *Haslam* Dep. ["I don't claim to be an expert on that at all"]); *id.* at 59-61. Moreover, outside of litigation, Furberg regularly has expressed disdain for the "class effect" concept, noting that there are no objective criteria for applying or defining the term. While "[d]rugs of a certain class may have a common therapeutic activity; [] they may differ substantially in terms of safety." Markel Decl., Ex. 7 at 448 (Furberg *Haslam* Dep.); *see also id.* at 458-59 (admitting many drugs in a class have different effects, including Bextra); Markel Decl., Ex. 5 AT 119 (EVALUATING CLINICAL RESEARCH); Markel Decl., Ex. 124 at 1456 (Furberg & Pitt, J. AM. COLL. CARDIOL. 2001;37:1456-60); Markel Decl., Ex. 14 at IV-15 (Furberg, CLIN. CARDIOL. 2000;23;7 Suppl. 4:IV15-19); Markel Decl., Ex. 16 at 1202 (Furberg et al., LANCET 1999;354:1202-04). Bennett agrees that in assessing thrombotic risk, it is methodologically inappropriate to extrapolate from one selective COX-2 inhibitor to another. *See* Markel Decl., Ex. 3 at 209 (Bennett Dep., *In re Pfizer*).

in which he used an endpoint similar to APTC. *See id.* at 35, 131, 158; *see also id.* at 34 (admitting he has used the APTC endpoint in other publications and has called it useful). Further, Baruch, Plaintiffs' only cardiologist, testified that three of the six outcomes included in Furberg's Alzheimer's 001 endpoint (heart failure, angina pectoris, and atrial fibrillation) are not clotting events.

Likewise, Plaintiffs' mechanism expert, Joel Bennett, acknowledges that acceptance of the imbalance hypothesis also implies that the APTC endpoint – which he describes as commonly used in the medical community – is a valid endpoint to assess the thrombotic risk of selective COX-2 inhibitors. *See* Markel Decl., Ex. 3 at 70-71, 263-64 (Bennett Dep., *In re Pfizer* ["[I]t's been used over and over."]); *id.* at 263-64 (agreeing with FDA's decision to use the APTC endpoint in its analysis). Bennett concedes that the "imbalance" hypothesis never has been linked to non-clotting events such as arrhythmias, which Furberg includes in his composite endpoints. *See id.* at 486-87; Markel Decl., Ex. 161 at 239-40 (Baruch Dep. [noting that another of Furberg's outcomes, pulmonary edema, is only sometimes related to clotting]).

Using the APTC endpoint, the Alzheimer's 001 trial does not show that Celebrex is associated with a statistically significant increase in the risk of thrombotic events. Plaintiffs' experts, however, never analyze the Alzheimer's trial based on the APTC endpoint to avoid reaching this certain conclusion. Instead, Furberg and Plaintiffs' other experts fabricate a new "endpoint" that lumps together a number of medical conditions that are not biologically related to thrombotic events and are inconsistent with the biological basis for Plaintiffs' claims, the "imbalance" hypothesis. Furberg's manipulation of the endpoints utilized in his analyses is not reliable science and his opinions therefore should be excluded by this Court.

b. Furberg's Failure to Require Statistical Significance Means That His Methods Cannot Be Validated

As noted above, after qualified medical doctors have collected and classified events that are specified in advance according to an endpoint that has an accepted biological basis, statisticians help evaluate whether differences between groups are due to the play of chance. *See*

Markel Decl., Ex. 5 at 7 (EVALUATING CLINICAL RESEARCH). If the difference exceeds a pre-specified *p*-value, then the result is said to be "statistically significant"—that is, the result is unlikely to be the result of random sampling error or mere chance, although statistical significance does not necessarily establish that the relationship is causal. Choosing the *p*-value in advance guards against modifications to the *p*-value threshold after reviewing the results in order to declare statistical significance.

Furberg completely ignores the need to analyze data for statistical significance. Rather, he defined his research question as whether, before December 16, 2004 when the APC results became available, there was evidence of a "*scientifically* significant" cardiovascular risk associated with Celebrex. *See* Markel Decl., Ex. 1 at 8 (Furberg Rep. [emphasis added]). Apart from sounding like the phrase "statistically significant," Furberg's term is nothing more than his own arbitrary metric. Furberg admits that he did not use any accepted methodology or objective criteria to answer his question. *See* Markel Decl., Ex. 8 at 70-71, 169, 243-44 (Furberg Dep.). He also admitted that he is unable to define the term "error rate," let alone evaluate the error rates associated with a methodology based on something other than objective statistical standards. *Id.* at 74. As a result, Furberg's analyses cannot be replicated or validated and should be excluded. *See, e.g.*, *Stone*, 2002 WL 1046706, at *3 (excluding expert report offered by plaintiff because there were no means by which to validate the purported expert's hypotheses).[64]

c. Furberg Concedes That The Great Weight Of Statistically Significant Data Do Not Show that Celebrex Increases Thrombotic Risk

The same court that excluded Furberg's opinion as being the product of his subjective views rather than valid scientific methodology correctly observed that to be admissible, an

[64] For instance, with the Alzheimer's 001 trial, Furberg testified that he ignored all three of Plaintiffs' retained expert statisticians and instead asked a graduate student named Doug Case to calculate the *p*-values for his unprecedented composite endpoint. *See* Markel Decl., Ex. 8 at 147, 201 (Furberg Dep.). However, there is no written record of what calculations Mr. Case was asked to perform, what calculations Mr. Case actually performed, and what methodology or process he undertook to achieve the results reported by Furberg. As a result, none of Mr. Case's work can be replicated or validated by a third party.

expert's opinion must consider the totality of evidence, and "account[] adequately for obvious alternative explanations." *In re Rezulin*, 369 F. Supp. 2d at 425. In *In re Bextra*, Judge Breyer applied this principle and excluded one of plaintiffs' experts because he "reache[d] his opinion by first identifying his conclusion . . . and then cherry-picking" studies that supported that conclusion and "rejecting or ignoring the great weight of the evidence that contradicts his conclusion." 524 F. Supp. 2d at 1176. Furberg likewise has written that the results of any post hoc analysis "will be highly questionable" if the trials selected for analysis are not chosen in a way that researchers are blinded to their actual results. *See* Markel Decl., Ex. 10 at 299 (Furberg, STAT. MED. 1987;6:295-303; Markel Decl., Ex. 8 at 65 (Furberg Dep. ["If you set up criteria for study selection after you have them all to make them fit your biases, I think that makes the P value tenuous."]). He also testified that it is "particularly troubling" if a post hoc analysis is based only on the published literature. *See* Markel Decl., Ex. 8 at 64 (Furberg Dep.). In this case, however, Furberg only chose to review the trials that support his view that Celebrex is unsafe and only relied on the published literature. *See id.* at 253, 265-66.

Even after applying the flawed methodology described above, Furberg's post hoc analysis concludes that from among the hundreds of studies involving Celebrex, only the Alzheimer's 001 trial – a single small study consisting of sick, elderly patients taking two times the commonly used Celebrex dose – reached a statistically significant result before December 16, 2004. Furberg further admitted that even as to this lone study, Alzheimer's 001 only reaches statistical significance when you look at a "wide network [and] broad definition of cardiovascular events" that he chose to combine into one endpoint after he knew the results of the trial. *Id.* at 163. At his deposition, he even downplayed the statistical significance of his unique endpoint, calling the result "nominally" statistically significant and adding, "It's more of a signal to say – to flag that something may not be right here." *Id.*

Outside of litigation, Furberg has cited and relied on highly-regarded meta-analyses, which show that patients taking Celebrex have no greater risk of a heart attack than patients taking either Aleve (naproxen) or no arthritis medication at all. *See* Markel Decl., Ex. 73 at 1634

(Antman et al., CIRCULATION 2007;115:1634-42 [citing Kearney and McGettigan]). Furberg's remaining Celebrex opinions are based on his finding "signals" and "trends" from other trials, but no other statistically significant results that involve a valid thrombotic endpoint. *See, e.g.*, Markel Decl., Ex. 1 at 22 (Furberg Rep. [admitting CLASS was not statistically significant]).[65] Indeed, when viewed in the context of the totality of the evidence, Furberg's unprecedented, biologically invalid endpoint in Alzheimer's 001 is a stark outlier – the only statistically significant result out of hundreds of possible analyses of the Celebrex clinical trial data. *See* App., Figs. 4 & 5 (demonstrating that only Furberg's contrived endpoint in Alzheimer's 001 showed a statistically significant increase in risk prior to APC whether Celebrex is compared to non-selective NSAIDs or no medication at all).

Accordingly, Furberg effectively concedes that the totality of evidence – as opposed to the single endpoint in the single study on which Furberg focuses – shows no statistically significant difference in the rate of heart attacks and strokes for patients taking Celebrex as opposed to no NSAID at all. Furberg should not be permitted to opine that Celebrex is associated with thrombotic risk based on a single endpoint in a single study when the totality of the evidence plainly leads to the opposite conclusion. *See* App., Figs. 4 & 5.

3. Furberg's Unreliable Bextra Analysis

Furberg likewise should not be permitted to testify that Bextra is associated with thrombotic risk because his analysis of Bextra suffers from the same methodological flaws as his Celebrex analysis. Significantly, Furberg admits that there is no evidence of a statistically significant increase in the risk of thrombotic events such as heart attack and stroke with oral Bextra pills alone. While he reviews multiple trials involving Bextra pills, none of his analyses addresses a valid thrombotic endpoint. He then improperly conflates the effects of experimental,

[65] Furberg admits that there are no objective criteria, testable methods, or known error rates by which to determine what constitutes a signal or trend. *See* Markel Decl., Ex. 8 at 70 (Furberg Dep. ["I'm not aware of any objective criteria [defining a signal], either from Pfizer, or the FDA or elsewhere. I think a signal can just be a single case."]); *see also id.* at 244 (admitting he does not "know always whether safety signals are real or not").

intravenous parecoxib with the effects of oral Bextra pills, even though journals rejected his attempts to do so outside of litigation, he never evaluated the parecoxib data to see if such a comparison is valid, and he is not qualified to assess the unique physiological characteristics of patients in the parecoxib CABG surgery trials. Finally, even if Furberg's Bextra assumptions based on parecoxib were evidence-based, he admits – as he must – that those trials did not show a statistically significant increase in thrombotic risk.

a. Furberg's Failure to Use Consistent, Clinically Valid Endpoints

Furberg acknowledges that a clinical researcher should evaluate the totality of evidence and compare endpoints consistently across trials. *See* Markel Decl., Ex. 125 at 567 (Yusuf et al., EUR. HEART J. 1985;6:556-85 ["To be even moderately reliable, inference should be based on the totality of the available evidence, and not on outcome-dependent subsets of it . . . ."]); Markel Decl., Ex. 8 at 257 (Furberg Dep.).

When Furberg reviews Bextra clinical trials in this litigation, however, he engages in classic cherry-picking of studies and endpoints in order to reach his preferred result. He therefore changes his endpoint of interest from study to study – including by again choosing endpoints that are not indicative of thrombotic events, as with his Celebrex analysis – and selects only a narrow universe of the available trials to fit his pre-determined conclusion. The endpoints on which Furberg focuses range from: (1) heart attacks only – and no other thrombotic events – in Study 016, *see* Markel Decl., Ex. 8 at 130-31, 238 (Furberg Dep.); (2) certain cardio-renal events, including hypertension, proteinuria, renal insufficiency, edema, and congestive heart failure, in Study 061, *see* Markel Decl., Ex. 1 at 32 (Furberg Rep.); (3) other renal endpoints, including reduced renal perfusion/filtration, renal tubular dysfunction, and interference with blood pressure, in Study 047, *see id.* at 33; Markel Decl., Ex. 8 at 253-54 (Furberg Dep.); (4) edema and blood pressure – but not heart attacks – in Study 132 and Study 133, *see* Markel Decl., Ex. 8 at 273-74 (Furberg Dep.); *see also id.* at 275 (noting that he did not even attempt to analyze the risk of heart attack because he "looked at the numbers and they didn't make [him]

highlight anything"); and (5) all-cause mortality – while ignoring non-fatal heart attacks and other thrombotic events altogether – in Study 040. *See id.* at 262, 264-66 (admitting that he did not even attempt to determine whether any patient suffered a heart attack in the trial); Markel Decl., Ex. 1 at 39 (Furberg Rep.). In other words, Furberg uses *five different endpoints in reviewing six trials* – two of which were nearly identical studies, and none of which showed a statistically significant increase in thrombotic events such as heart attack and stroke.

Because he cannot identify a statistically significant result in any of the trials involving oral Bextra pills, Furberg repeatedly points to "trends" and "signals" related to events of all types and biological origin. *See* Markel Decl., Ex. 8 at 235-36, 241, 243-44 (Furberg Dep.). Indeed, Furberg stated that his "role was more to highlight signals and give illustrations" of signals, rather than to identify statistically significant increases in the risk of concrete medical outcomes. *Id.* at 248. At the same time, he concedes that there are no objective criteria, testable methods, or known error rates by which to determine what constitutes a signal or trend. *See id.* at 70, 169. Thus, Furberg cannot identify any evidence of a statistically significant increase in the risk of thrombotic events such as heart attacks and strokes with oral Bextra pills. As importantly, by cherry-picking the studies forming the basis of his opinion rather than considering the totality of available data, and selectively choosing and changing endpoints to reach a desired result, his analysis plainly fails to meet the reliability criteria established in *Daubert* and its progeny, and the Court therefore must exclude his opinions.

b. Furberg Improperly Conflates the Effects of Intravenous Parecoxib with the Effects of Bextra

With no reliable data to support his pre-existing opinions related to Bextra, Furberg then concludes – without any objective standards or qualifications in the relevant field – that very high doses of intravenous parecoxib after CABG surgery have the same cardiovascular effects as oral Bextra pills taken for arthritis.[66] Furberg is not a cardiologist or pharmacologist, and he

[66] Furberg also lacks sufficient knowledge to compare Bextra to other selective COX-2 inhibitors. Furberg concedes that he cannot describe the molecular differences between Bextra and Vioxx, nor could he identify specific

offers no reliable methodology to demonstrate that the medications have identical effects on patients taking them. He did not even attempt to explain the actual evidence that reveals significantly different effects, such as their divergent effect on blood pressure, *see id.* at 217; Markel Decl., Ex. 7 at 189-90, 192, 237 (Furberg Dep., *Haslam v. Pfizer*); notes 36 & 39 *supra*, even though he has written repeatedly outside of litigation that differences between medications can result in different safety profiles.[67] In fact, Furberg even has noted that the effects of intravenous prodrugs can differ substantially from the effects of oral forms of the same medication.[68]

Similarly, Furberg did not analyze the numerous physiological differences between patients undergoing CABG surgery and those in the general arthritis population because he is not qualified to do so. *See* Markel Decl., Ex. 1 at 42 (Furberg Rep.); Markel Decl., Ex. 8 at 246-47 (Furberg Dep.); Markel Decl., Ex. 7 at 189-92 (Furberg Dep., *Haslam v. Pfizer*).[69] He is not an expert on cardiovascular anesthesiology or how CABG surgery affects the body's clotting and circulatory systems. *See* Markel Decl., Ex. 7 at 51-52, 58-61 (Furberg Dep., *Haslam v. Pfizer*). He never has performed CABG surgery and cannot describe how it is performed. *See* Markel

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data to suggest Bextra is less safe than Celebrex, nor did he even attempt to evaluate the different effects of oral Bextra pills compared to intravenous parecoxib. Markel Decl., Ex. 7 at 61, 189-90, 192, 237, 402-04 (Furberg Dep., *Haslam v. Pfizer*). He also failed to address long-term observational data that shows an increased risk with Vioxx, but not Bextra or Celebrex. *See, e.g.*, Markel Decl., Ex. 91 (Solomon S. et al., ARTH. & RHEUM. 2006; 54:1378-89). Ultimately, Furberg admits that it is improper to combine Vioxx data with Bextra data to draw conclusions about Bextra. Markel Decl., Ex. 7 at 282-83 (Furberg Dep., *Haslam v. Pfizer*).

[67] *See* note 12 *supra*; *see also* Markel Decl., Ex. 5 at 116 (EVALUATING CLINICAL RESEARCH); Markel Decl., Ex. 124 at 1456 (Furberg & Pitt, J. AM. COLL. CARDIOL. 2001;37:1456-60).

[68] *See* Markel Decl., Ex. 14 at IV-18 (Furberg, *Class Effects and Evidence-Based Medicine*, CLIN. CARDIOL. 2000;23;7 Suppl. 4:IV15-19 ("[D]rugs within a therapeutic class may also have substantially different pharmacologic properties. . . . Pharmacokinetic differences include whether a drug is an active compound or a prodrug requiring conversion to an active metabolite . . . ."); *see also* Markel Decl., Ex. 4 at 181-82 (FUNDAMENTALS OF CLINICAL TRIALS).

[69] Those who did analyze the different effects of intravenous parecoxib and oral Bextra pills and the differences between CABG surgery and arthritis populations – such as Pfizer's experts Dr. Frank Sellke, and Dr. Barry Massie, whose opinions with respect to CABG surgery are unrebutted – identified numerous ways in which parecoxib is distinct from Bextra. *See* Markel Decl., Ex. 127 at 13 (Sellke Rep. [noting that parecoxib *reduces* blood pressure, while Bextra increases blood pressure in some patients at some doses]); *id.* at 21, 24 ([noting the many ways in which CABG surgery patients differ from ordinary patients]); Markel Decl., Ex. 128 at 35-36 (Massie Rep. [same]).

Decl., Ex. 7 at 51 (Furberg Dep., *Haslam v. Pfizer*). Furberg ignores those differences between CABG patients and arthritis patients even though outside the courtroom he regularly admonishes clinical researchers to take great care when extrapolating from the patient population in a clinical trial to patients generally. *See* Markel Decl., Ex. 4 at 37 (FUNDAMENTALS OF CLINICAL TRIALS); Markel Decl., Ex. 15 at 572 (Furberg, HEART 2002;87:570-74); Markel Decl., Ex. 17 at 88 (Furberg, POSTGRADUATE MEDICINE: A QUARTER-CENTURY OF BETA BLOCKADE (1988)); Markel Decl., Ex. 126 at 921-22 (Alderman et al., AM. J. HYPERTEN. 2002;15:917-23).[70]

The results from CABG-2 further confirm that it is inappropriate to extrapolate the data derived from studies involving high-dose intravenous parecoxib to Bextra. In that study, while the group that took very high doses of intravenous parecoxib was at an increased risk of thrombotic events, the group receiving oral Bextra pills only did *not* demonstrate a statistically significant increased risk of thrombotic events compared to the placebo group. Markel Decl., Ex 87 at 1087 (Nussmeier). Similarly, even when results from the parecoxib / oral Bextra pills group were combined with results from the oral Bextra pills only group – as Furberg did in his editorial – the difference in thrombotic events compared to the placebo group was not statistically significant. *See id.*

In short, Furberg lacks expertise in any of the fields of interest such that he would be qualified – and he employed no discernable methodology that would permit him – to opine that very high doses of intravenous parecoxib after CABG surgery have the same cardiovascular effects as oral Bextra pills taken for arthritis. As a result of his lack of qualifications in this area and the absence of any (let alone a reliable) methodology supporting what is nothing more than his subjective Bextra opinion, the Court should exclude his testimony. *Daubert*, 509 U.S. at 589-90.

[70] Indeed, in light of these different drug effects and populations, when Furberg attempted to submit an article for publication that combined data from the parecoxib CABG surgery trials with data from arthritis trials involving oral Bextra pills, all the journals to which he submitted his analysis rejected it. *See* Markel Decl., Ex. 7 at 313-16, 320 (Furberg Dep., *Haslam v. Pfizer*).

c. The CABG Surgery Trials Do Not Show an Increase in Thrombotic Risk

Finally, even if Furberg could extrapolate reliably from the parecoxib CABG surgery trials to patients taking oral Bextra pills outside that unique setting, he admits – as he must – that the parecoxib CABG surgery trials did not show a statistically significant increase in the risk of thrombotic events for patients taking only oral Bextra pills. Outside of this litigation, Furberg's editorial indicates that neither parecoxib CABG surgery trial showed a statistically significant increase in thrombotic risk with respect to patients taking only oral Bextra pills – even when Furberg lumped together the intravenous parecoxib / oral Bextra pill group of the CABG-2 study with the oral Bextra pill only group. *See* Markel Decl., Ex. 20 at 249 (Furberg et al., CIRCULATION 2005;111:249); *see also* Markel Decl., Ex. 82 at 1488 (Ott); Markel Decl., Ex. 87 at 1087 (Nussmeier).

Accordingly, Furberg should not be permitted to opine that Bextra is associated with thrombotic risk when the two studies upon which he primarily relies, CABG-1 and CABG-2, do not demonstrate statistically significant differences between patients taking oral Bextra pills and those taking standard medication for surgical pain, and when the totality of the evidence plainly leads to the opposite conclusion. *Lust*, 89 F.3d at 596 (noting that an expert may not "'pick and chose' [sic] from the scientific landscape and present the Court with what he believes the final picture looks like") (citation omitted); *see* App., Fig. 6 (demonstrating that none of the Bextra or parecoxib trials showed a statistically significant increase in risk when comparing Bextra to non-selective NSAIDs or no medication).

C. Kronmal's Methods Are Unreliable And Therefore His Opinions Are Inadmissible

Kronmal conceded that his assignment was biased from the beginning. Plaintiffs' counsel asked him to assume that Celebrex and Bextra increased the risk of thrombotic cardiovascular events and to find evidence in support of that assumption before December 2004. *See* Markel Decl., Ex. 12 at 49-50, 254 (Kronmal Dep.). His assignment therefore required him to ignore the great weight of evidence demonstrating that Celebrex and Bextra are not associated

with thrombotic risk. Kronmal performed that assignment by cherry-picking his data and, even though not remotely qualified to do so, making up composite endpoints for assessing thrombotic risk in order to achieve the results mandated by Plaintiffs' counsel. As a result, his testimony and opinions are not reliable and should be excluded under Rule 702.

1. Kronmal Uses Shifting, Invalid Endpoints In His Celebrex Analysis

Kronmal, like Plaintiffs' three other statisticians, has no credentials in medicine, does not treat patients, is not a cardiologist, and is not qualified to assess whether it is biologically appropriate to group certain types of cardiovascular events in analyzing clinical trial data. *See* Markel Decl., Ex. 12 at 123-27, 129 (Kronmal Dep.). It therefore is unsurprising that outside of this litigation, Kronmal has collaborated with cardiologists and other medical specialists to examine the cardiovascular effects of other medications and regularly has employed composite endpoints that include stroke.[71] This includes use of the APTC endpoint of heart attack, stroke and coronary death. *See* Markel Decl., Ex. 63 at 209 (Smith et al. ARCH. INTERN. MED. 2002;162:209-16).

Notwithstanding his lack of qualifications to choose an endpoint for assessing thrombotic risk and his past use of the APTC endpoint, in this case Kronmal declines to use either the conventionally accepted APTC endpoint or to include stroke as an outcome as a part of any endpoint in his analysis. *See* Markel Decl., Ex. 12 at 356 (Kronmal Dep.). Kronmal opposes the use of the APTC endpoint here because – with the benefit of hindsight – he believes that COX-2 inhibitors do not increase the risk of stroke, and including stroke in a composite endpoint supposedly would dilute any analysis of data that existed before 2004. *See id.* at 245-46, 250 (noting that he would not include stroke in a composite endpoint because "I don't think this class

[71] For example, in a 2008 study, Kronmal and his co-authors' main outcome measure of risk was "cardiovascular disease events," including coronary heart disease, stroke and fatal cardiovascular disease. Markel Decl., Ex. 62 at 1333 (Folsom et al., ARCH. INTERN. MED. 2008 June 23; 168(12):1333-39). In a 2003 study, Kronmal and others used an endpoint of "combined cardiovascular events" consisting of "angina, myocardial infarction, transient ischemic attack, ischemic stroke, peripheral vascular disease, or death attributable to atherosclerotic disease." Markel Decl., Ex. 129 at 2022 (Heckbert et al., CIRCULATION 2003;107:2021-24).

of drugs causes stroke"). In other words, rather than pre-specifying a particular endpoint and employing an accepted approach that is used in the cardiovascular research community, Kronmal reviewed the data first, looked for any imbalances in any "heart-related" outcomes, and then used those outcomes to shape an endpoint. *Id.* at 60-61. Even Plaintiffs' experts disdain such a post hoc approach, which is the type of cherry-picking of data supportive of a preferred outcome, *see* Section I.C.2 *supra*, and which led Judge Breyer to exclude expert testimony in *In re Bextra*.

Kronmal's desire to exclude stroke is based on his hindsight bias and not a valid medical rationale that existed when any of the Celebrex trial results first became available. He lacks the formal training and medical expertise to assess whether an endpoint is medically valid. Markel Decl., Ex. 12 at 123-24 (Kronmal Dep.). He also does not propose any biological explanation as to how COX-2 inhibitors could cause heart attacks, but not strokes. Likewise, he does not suggest any medical basis to link a heart rhythm abnormality like arrhythmia with a clot-induced event such as heart attack, yet at the same time to exclude other clot-induced events such as stroke. In fact, Kronmal disclaims any knowledge regarding the biological basis for any of Plaintiffs' claims. *See id.* at 297-98 (noting that "there's very little evidence . . . as to what causes the side effects that are associated with these drugs" and concluding that "anybody who tells you they know the mechanism is speculating").

Indeed, Kronmal changes his endpoint from trial to trial to fit his preordained conclusion, ranging from heart attacks only, *see* Markel Decl., Ex. 2 at 24 (Kronmal Rep. [evaluating CLASS and SUCCESS, but admitting the differences were not statistically significant]), to heart attacks plus sudden death, *see* Markel Decl., Ex. 12 at 244-45, 248 (Kronmal Dep.), to an amalgam of heart attacks, sudden death, congestive heart failure, and arrhythmias, *see id.* – all of which exclude stroke and none of which have been endorsed by qualified cardiologists. Kronmal fails to cite any paper in the literature where the various combined endpoints he proposes were used as primary measures of the cardiovascular safety of Celebrex before 2004, let alone employed consistently across any of the Celebrex trials before 2004. *See generally* Markel Decl., Ex. 2 (Kronmal Rep.).

Moreover, using either the APTC endpoint or his preferred endpoint of heart attacks alone, Kronmal concedes that the Alzheimer's 001 study did not show a statistically significant difference between patients taking Celebrex and those taking a placebo pill. *See id.* at 23. It is only when Kronmal goes beyond his field of statistics and expands the endpoint to include all "heart related events" regardless of their biological dissimilarities – including cardiovascular disorders, heart rate and rhythm disorders, and myocardial, endocardial and valve disorders – that he can contrive a statistically significant result for this trial. *See id.* Tellingly, Kronmal admits that the APC trial, in December 2004, was the first trial to show a statistically significant increase in the risk of thrombotic cardiovascular events for Celebrex compared to placebo. *See* Markel Decl., Ex. 12 at 345-46 (Kronmal Dep.).

Kronmal's analysis suffers from the same methodological defect that plagues Madigan and Furberg's analyses as well. Rather than focus on a biologically legitimate, conventionally accepted endpoint and apply that endpoint consistently across trials, Kronmal, like Plaintiffs' other experts, changes the endpoint with each study analyzed in order to contrive evidence of thrombotic risk. Such an approach violates well established principles for conducting an analysis of clinical study data, including those articulated by Plaintiffs' own experts. Indeed, Kronmal's analyses are rooted in an attempt to manipulate the data to achieve a desired result, and his opinions therefore should be excluded as unreliable under Rule 702.

2. <u>Kronmal's Unreliable Bextra Analysis</u>

Kronmal's Bextra analysis is equally unreliable, although for different reasons: he engages in a slipshod, unreliable method of data collection and then offers opinions based on such data by making assumptions involving cardiovascular and pharmacological issues which, as a statistician, he plainly is not qualified to make. First, although Plaintiffs' experts agree that an essential element of a reliable statistical analysis involves appropriate collection of data from all relevant sources, Kronmal's opinions regarding Bextra are based on a review only of the electronic data files and a handful of study reports. *See* Markel Decl., Ex. 2 at 3-4 (Kronmal

Rep.). Kronmal's unfamiliarity with the data files – combined with his lack of qualifications to make clinical judgments regarding adverse events – led him to claim originally that he had identified serious cardiovascular events that Pfizer missed in its study reports. *See id.* at 9-10; Markel Decl., Ex. 12 at 125 (Kronmal Dep. [admitting he is not a cardiologist]; *id.* at 36-37, 40 (admitting he did not consult with a cardiologist or anyone else to decide what endpoints should be examined). In his report, Kronmal claimed that if these events had been included, many of the differences would have reached statistical significance. *See* Markel Decl., Ex. 2 at 9-10 (Kronmal Rep.).

At his deposition, however, Kronmal could not identify the missing events and retracted his concerns. *See* Markel Decl., Ex. 12 at 304-11 (Kronmal Dep.). In fact, he admitted that his report was "maybe a little too strong a statement" and that he did not "know for certain" whether the events met the criteria to be counted as adverse events. *Id.* at 310-11. Ultimately, Kronmal concedes that no trial of oral Bextra pills shows a statistically significant increase in the risk of thrombotic events like heart attacks and strokes. *See* Markel Decl., Ex. 2 at 11-12 (Kronmal Rep. [conceding non-significant results compared to placebo or naproxen]).

Second, for his conclusions regarding the effects of oral Bextra pills Kronmal relies heavily on data from the high-dose, intravenous parecoxib CABG surgery trials. Kronmal, however, is a statistician and is not qualified to make medical judgments about whether it is appropriate to compare the physiology of patients undergoing CABG surgery to that of patients in the general arthritis population. *See* Markel Decl., Ex. 12 at 6, 124-27 (Kronmal Dep. [admitting he does not have a medical degree, is not a cardiologist, and never would treat a patient]). Kronmal also failed – and is not qualified – to evaluate how the effects of intravenous parecoxib differ from those of oral Bextra pills, or to offer any reliable methodology to demonstrate that the thrombotic effects are the same. *See id.* at 317-18; *see generally* Markel Decl., Ex. 2 (Kronmal Rep.).

Even if Kronmal were qualified to assess whether the parecoxib CABG surgery trials could demonstrate an increased thrombotic risk related to oral Bextra, which he is not, Kronmal

admits that there is no statistically significant increase in thrombotic risk in the parecoxib CABG-1 trial. *See* Markel Decl., Ex. 2 at 9 (Kronmal Rep. [conceding non-significant results for thrombotic events in parecoxib CABG-1 trial]). He also admits that the parecoxib CABG-2 study did not show a statistically significant increase in risk for the group taking oral Bextra pills only. *See* Markel Decl., Ex. 12 at 334-35 (Kronmal Dep.).

Accordingly, Kronmal's Bextra opinions do not satisfy the criteria for admissibility under Rule 702. Kronmal reaches his conclusions based on data collected by unreliable methods, and makes assumptions – which he is not qualified to make – about the relevance of data from the administration of high-dose, experimental intravenous parecoxib to oral Bextra pills. While these flaws in and of themselves should be sufficient to exclude Kronmal's Bextra opinions, his opinions also are unreliable because he ignores the totality of the Bextra data, relying instead on select studies (involving parecoxib, not Bextra, administered to patients undergoing CABG surgery), and he further concedes that even these CABG studies do not demonstrate a statistically significant thrombotic risk associated with oral Bextra pills.

D. Baruch Is Not Qualified To Offer His Opinions In This Case

Baruch is a rebuttal expert and the only cardiologist among Plaintiffs' six experts. Markel Decl., Ex. 61 at 1 and Curriculum Vitae (Baruch Rep.). He attempts to rebut Pfizer's experts, Drs. Sellke, Massie, Weintraub and Fitzpatrick, who opine that it is not scientifically reliable to draw conclusions regarding whether oral Bextra pills are associated with thrombotic risk based on data derived from the parecoxib CABG surgery trials. Markel Decl., Ex. 61 at 1, 3, 5, 8-9 (Baruch Rep.).[72]

[72] While Baruch's report contains opinions related to the "imbalance" hypothesis, he admits he is not an expert in that field. *See* Markel Decl., Ex. 161 at 235-36 (Baruch Dep. ["It is not my area of expertise."]); *id.* at 232, 237.

1. Baruch Is Not Qualified to Offer Opinions About the Parecoxib CABG Surgery Trials

It is well settled that "a district court must continue to perform its gatekeeping role by ensuring that the actual [expert] testimony does not exceed the scope of the expert's expertise, which if not done can render expert testimony unreliable under Rule 702." *Wheeling Pitt. Steel*, 254 F.3d at 715. Here, Baruch admits that never in his career has he performed – or even assisted in performing – a CABG surgery. Markel Decl., Ex. 161 at 237-38 (Baruch Dep.). Baruch's most direct involvement with a CABG surgery was being "in the room" once when the procedure was performed more than twenty years ago when he was in medical school. *Id.* at 237-38. Baruch also testified that he is not an expert on how CABG surgery affects clotting in the blood. *See id.* at 204-06.

In his report, Baruch says that the "claim that parecoxib somehow is different from oral [Bextra] has no scientific basis." Markel Decl., Ex. 61 at 6 (Baruch Rep.). Baruch admitted, however, that this opinion is based on what he views as admissions by Pfizer that intravenous parecoxib and Bextra are based on the same molecular structure. Markel Decl., Ex. 161 at 192-96 (Baruch Dep.); *see also* Markel Decl., Ex. 61 at 6 (Baruch Rep.). Molecular differences aside, Baruch has not done any research on or analysis of the effects of intravenous parecoxib compared to oral Bextra pills, including their pharmacodynamic and pharmacokinetic differences[73] – such as the concentrations they reach in the human body[74] – and their different cardiovascular effects. Markel Decl., Ex. 161 at 189-90, 192 (Baruch Dep.).[75] He also fails to

[73] Pharmacodynamics is the study of "what a drug does to the body." Markel Decl., Ex. 130 at 1291 (Ou et al., *Cardiac Drug Adverse Effects and Interactions*, in MAYO CLINIC CARDIOLOGY (3d ed., 2007)). Pharmacokinetics "comprises the process of drug absorption, distribution, metabolism and elimination." Markel Decl., Ex. 130 at 1189 (Jahangir et al., *Principles of Pharmacokinetics and Pharmacodynamics, in* MAYO CLINIC CARDIOLOGY (3d ed., 2007)).

[74] Baruch admits that the method of administration can affect the blood levels of a medication, but he does not know how the blood levels differ with intravenous parecoxib compared to oral Bextra pills. *See* Markel Decl., Ex. 161 at 190-92 (Baruch Dep.). When asked whether different blood levels resulting from intravenous parecoxib or Bextra pills could result in different thrombotic effects, Baruch admitted that he did not know. *See id.* at 196-97.

[75] Baruch therefore does not rebut the reports of Drs. Sellke and Massie with respect to the different cardiovascular effects of intravenous parecoxib and oral Bextra pills – particularly the medications' different effects on blood pressure. *See* notes 36 & 39 *supra*.

consider or explain data that do not support his opinion, such as the trial of high-dose, experimental, intravenous parecoxib followed by high-dose oral Bextra pills in general surgery patients that did not show an increased risk. *See* Markel Decl., Ex. 90 at 523 (Nussmeier, et al., ANESTHESIOLOGY 2006;104:518-28).

Finally, Baruch does not account for – or even acknowledge – the physiological differences between patients undergoing CABG surgery and the general population, nor does he offer any explanation or methodology to evaluate the similarities and differences between those populations. *See* Markel Decl., Ex. 61 at 6-8 (Baruch Rep.). At his deposition, Baruch conceded that the mechanism of heart attacks in post-CABG patients is "not exactly the same" as in the general population and that, as opposed to a clotting mechanism, heart attacks in post-CABG patients could involve many different mechanisms. Markel Decl., Ex. 161 at 205-06 (Baruch Dep.). Baruch's unsupported opinion, which he is not qualified to offer, also stands in stark contrast to the opinion offered by another of Plaintiffs' experts, Joel Bennett, who concedes that the physiology of CABG surgery patients is entirely distinct from the general population. *See* Markel Decl., Ex. 3 at 328-29 (Bennett Dep., *In re Bextra*).

As a result, not only are Baruch's opinions undermined by Plaintiffs' own mechanism expert, but Baruch plainly is not qualified to offer opinions in the first place regarding whether data derived from the high-dose, intravenous parecoxib CABG surgery trials is relevant to assess whether Bextra is associated with thrombotic risk. This Court's gatekeeper function requires the exclusion of such testimony.

2. Baruch's Unreliable Conclusions Regarding the Parecoxib CABG Surgery Trials

As significantly, Baruch's statements about the conclusions that can be reached from the CABG trials with respect to whether Bextra is associated with thrombotic risk are unreliable and should be excluded. Baruch's report indicates that the CABG-1 trial "revealed a statistically significantly greater incidence of cardiovascular/thromboembolic events in parecoxib/valdecoxib treated patients, including a more than twofold increase in myocardial infarction." Markel Decl.,

Ex. 61 at 4 (Baruch Rep.). When asked to support that statement, however, Baruch admitted that his source, the published article on CABG-1, did not contain any statistically significant findings with regard to cardiovascular or thromboembolic events. *See* Markel Decl., Ex. 161 at 197-99 (Baruch Dep. ["I can't find it."]; *id.* at 200-01 [agreeing CABG-1 not statistically significant]; *see also* Markel Decl., Ex. 82 (Ott). As a result, Baruch has no basis for the opinion in his report regarding the CABG-1 surgery trial, which should thus be inadmissible.

With respect to CABG-2, Baruch's report states that there was a statistically significant increase in the risk of certain cardiovascular events for patients receiving very high doses of intravenous parecoxib followed by high-dose oral Bextra pills. *See* Markel Decl., Ex. 61 at 5 (Baruch Rep.). Yet Baruch neglects to mention that there was no statistically significant increase in risk among patients who took oral Bextra pills only, even when those patients were combined with the parecoxib patients. *See* Markel Decl., Ex. 87 at 1087 (Nussmeier).

Further, although Baruch testified that he "predominantly" relies on heart attacks, strokes, and cardiovascular deaths in his analysis of Bextra and Celebrex, he made no attempt to apply those endpoints to the CABG-2 results. Markel Decl., Ex. 161 at 147 (Baruch Dep.); *see* Markel Decl., Ex. 61 at 9-10 (Baruch Rep.). He also said that he was unaware that Furberg had reviewed both parecoxib CABG surgery trials for his editorial and found that neither CABG trial individually showed a statistically significant increase in heart attacks and strokes. *See* Markel Decl., Ex. 161 at 199-201 (Baruch Dep.); *see also* Markel Decl., Ex. 20 at 249 (Furberg, et al., CIRCULATION 2005;111:249 [stating that the CABG surgery trials "did not reach conventional levels of statistical significance"]).

Ultimately, Baruch had to concede that there are no clinical trials yielding a finding that Bextra, in the absence of intravenous parecoxib, was associated with a statistically significant increase in the risk of heart attack, stroke, or cardiovascular death. Markel Decl., Ex. 161 at 214-15 (Baruch Dep.). He also is not aware of any analysis of clinical trials before December 2004 showing a statistically significant association between oral Bextra pills and heart attack, stroke, or cardiovascular death. *Id.* at 215. In light of these admissions, coupled with the absence of any

methodology employed by Baruch in forming his opinions, his opinions regarding the two parecoxib CABG surgery trials are unreliable and therefore inadmissible under Rule 702.

E. Bennett's Opinions Are Speculative And Therefore Inadmissible

Bennett is Plaintiffs' mechanism expert.[76] He opines on the validity of the "imbalance" hypothesis which, again, posits that selective COX-2 inhibitors tip the balance of prostacyclin (an anti-clotting agent) and thromboxane (a pro-clotting agent) and other pro-clotting agents in a way that makes platelets in the blood more likely to clot, thereby increasing the risk of clotting events like heart attack and stroke. *See* Markel Decl., Ex. 9 at 1, 5 (Bennett Rep.). Where a purported expert witness relies on a theory or hypothesis which is not objective and cannot be validated, but rather constitutes subjective speculation, courts consistently have excluded such expert's testimony as insufficiently reliable under Rule 702 and *Daubert*. *See, e.g.*, *Stone*, 2002 WL 1046706, at *3. Bennett's opinions regarding the imbalance hypothesis are rank speculation, as he concedes, requiring the Court to exclude these opinions under Rule 702.

Before forming his opinions, Bennett did not consider, research, or rule out numerous other potential mechanisms by which selective COX-2 inhibitors might increase the risk of thrombotic events. *See* Markel Decl., Ex. 3 at 476-78, 822-23 (Bennett Dep., *In re Bextra*). He concedes that no test ever has demonstrated that Celebrex causes an "imbalance" between prostacyclin and thromboxane in human arteries or that such an imbalance is capable of acting directly on human arteries to enhance clot formation. *See id.* at 144-45. He also is not aware of any clinical trials where investigators measured prostacyclin and thromboxane, let alone the so-called "imbalance" between the two. *Id.* at 691-92. Bennett has admitted that the "imbalance" hypothesis "remains a prediction" and "is not definitive evidence." *Id.* at 534, 540. Indeed, in two separate publications, Bennett and his co-authors said only that the purported imbalance effect has been "speculated." *Id.* at 421-22, 472-73; Markel Decl., Ex. 131 at 1714 (Bennett et

[76] Bennett has not yet been deposed in this litigation because Plaintiffs' counsel canceled Bennett's deposition for health reasons and has not yet provided a new date. The following is taken from his Rule 26 report in this case and testimony from the Celebrex and Bextra product liability litigation.

al., CIRCULATION 2005;111:1713-16); Markel Decl., Ex. 73 at 1637 (Antman et al., CIRCULATION 2007;115:1634-42); *see also Golod v. La Roche*, 964 F. Supp. 841, 860 (S.D.N.Y. 1997) (holding that proposed expert testimony was inadmissible because "although [it] may be biologically plausible, it does not constitute 'scientific knowledge' within the meaning of *Daubert* . . . it is at most, scientifically-grounded speculation: an untested and potentially untestable hypothesis").[77]

Moreover, while some of Plaintiffs' experts rely on Bennett's "imbalance" theory, *see* Markel Decl., Ex. 97 at 1 (Madigan Rep.); Markel Decl., Ex. 61 at 11 (Baruch Rep.), others, like Kronmal and Furberg, have expressed skepticism about its validity. For instance, Kronmal testified that "anybody who tells you they know the mechanism is speculating." Markel Decl., Ex. 12 at 298 (Kronmal Dep.); *see also* Markel Decl., Ex. 7 at 202-04 (Furberg Dep., *Haslam v. Pfizer* [testifying that he does not view the "imbalance" hypothesis as useful to his analysis]). Similarly, in its 2005 analysis, FDA rejected the "imbalance" hypothesis on the ground that selective COX-2 inhibitors "have been indistinguishable" from non-selective NSAIDs on the basis of thrombotic risk. Markel Decl., Ex. 55 at 8 (FDA Decision Mem.).

Because Bennett concedes that the "imbalance" hypothesis is speculative, has not been proven, and cannot be validated, and Plaintiffs' other experts confirm that the hypothesis is nothing more than speculation, Bennett's opinions are not admissible under Rule 702.[78]

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[77] *See also Pretter v. Metro N. Commuter R.R. Co.*, No. 00 CIV. 4366, 2002 WL 31163876, at *1 (S.D.N.Y. Sept. 30, 2002) (excluding expert testimony because it was "unscientific conjecture masquerading as science"); *Faryniarz*, 2002 WL 1968351, at *3 (noting that "conclusions regarding causation [that] are incapable of being tested or challenged" are "precisely the type of evidence Rule 702 was intended to exclude").

[78] Although he is not a cardiologist, epidemiologist, or biostatistician, *see* Markel Decl., Ex. 3 at 38-39, 86 (Bennett Dep., *In re Bextra*), Bennett concedes that the announcement of the APC results in December 2004 was the first evidence of a statistically significant increase in thrombotic risk for patients taking Celebrex. *See* Markel Decl., Ex. 3 at 103-04 (Bennett Dep., *In re Bextra*). Bennett made that concession after analyzing the totality of the Celebrex data in what he believed to be a thorough and reliable way. *Id.* at 385-86. Outside of litigation, Bennett has cited and relied on highly-regarded meta-analyses, which show that patients taking Celebrex have no greater risk of a heart attack than patients taking either Aleve (naproxen) or no arthritis medication at all. *See* Markel Decl., Ex. 73 at 1634 (Antman et al., Circulation 2007;115:1634-42 [citing Kearney and McGettigan]); *see also* Markel Decl., Ex. 9 at 3 & App. B (Bennett Rep.); Markel Decl., Ex. 3 at 249-50, 515-16, 572-73 (Bennett Dep., *In re Bextra*).

F. Jewell's Criticisms Of Dr. Wei Are Irrelevant

Jewell has spent the majority of his career working on statistical issues related to observational studies, virtually no time working on clinical trials involving medications, and no time working on meta-analyses of clinical trials. *See* Markel Decl., Ex. 19 at 11-16, 25-27 (Jewell Dep.). Nonetheless, Plaintiffs retained Jewell, their third statistician, as a rebuttal expert to critique a meta-analysis of clinical trials performed by Pfizer's expert biostatistician, Dr. L.J. Wei. *Id.* at 29; Markel Decl., Ex. 102 at 3 (Jewell Rep.); *see also* Markel Decl., Ex. 19 at 132-33 (Jewell Dep. [noting that he did not perform his own meta-analysis]).[79] One of Jewell's criticisms is that Wei should have used a one-sided p-value, which would make Celebrex look statistically less safe for the heart. Plaintiffs' own expert Furberg refers to Jewell's method as "cheating" because it assumes an increased risk and artificially biases the data against Celebrex. Markel Decl., Ex. 7 at 123 (Furberg Dep., *Haslam v. Pfizer*). Jewell raised these exact same criticisms in the product liability litigation before Judge Breyer, but when Plaintiffs moved to exclude Wei based on Jewell's claims, Judge Breyer denied Plaintiffs' motion. *See In re Bextra*, 524 F. Supp. 2d at 1184. More importantly, Jewell offers no opinions that there was reliable, statistically significant evidence of a thrombotic risk before December 16, 2004 when APC was made public. *See generally* Markel Decl., Ex. 102 (Jewell Rep.). As a result, his analyses are irrelevant for purposes of this motion.

[79] Like FDA, Wei conducted a detailed meta-analysis of the Celebrex clinical trials that used the APTC endpoint and found no statistically significant evidence of an increased thrombotic risk for patients taking Celebrex compared to patients taking another NSAID or no NSAID at all until December 16, 2004, when the APC trial results became available. *See* Markel Decl., Ex. 133 at 33-36 (Wei Rep.).

CONCLUSION

In sum, Plaintiffs' experts' opinions related to the thrombotic safety of Celebrex and Bextra before December 16, 2004 should be excluded as a matter of law under Rule 702. According to FDA, Judge Breyer, and all worldwide clinical researchers who have used reliable methods to analyze the Celebrex data, the APC trial was the first time that a Celebrex clinical trial showed that patients taking Celebrex experienced statistically more heart attacks and strokes than patients taking sugar pills. Moreover, since the APC data became available to Pfizer and the public, no other Celebrex clinical trial has replicated the results of APC. Similarly, no Bextra clinical trial showed a statistically significant increase in the risk of thrombotic events such as heart attacks and strokes for patients taking oral Bextra.

Now, for the first time, it is only through a series of unprecedented, post-hoc methods – never used in actual clinical research – that Plaintiffs' experts are able to fabricate a few numerical differences that cross the threshold of statistical significance. These numerical differences are created by including irrelevant data from other medications, manipulating composite endpoints that do not reliably measure heart attack and stroke risk, and employing data collection methods that ignore certain relevant events and incorrectly classify other relevant events. These unreliable methods create results that artificially bias the data against both Celebrex and Bextra.

Thus, Plaintiffs' experts' methods are not employed with the same level of intellectual rigor that characterizes the practice of experts in the clinical research field. The Court should grant Pfizer's motion and exclude any expert opinion that the Celebrex or Bextra data showed reliable evidence of an increased risk of heart attacks or strokes before December 16, 2004.

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APPENDIX

FIGURE 1

Madigan's Shifting Methodologies

	Methods Used in Peer-Reviewed Literature on COX-2 Inhibitors	Methods Used in Madigan's Vioxx Report	Methods Used in Madigan's Celebrex Report	Madigan Celebrex Testimony
Were both original study reports and electronic sources of data searched for information?	Yes[1]	Yes[2]	No. Arbitrarily restricted analysis to studies with electronic databases[3]	Admitted he restricted analysis to studies with electronic databases provided to him by the Plaintiffs[4]
What primary endpoint was used for the meta-analysis?	Used several well accepted endpoints[5]	Used several well accepted endpoints[6]	Used a combination of sudden death and myocardial infarction[7]	Agreed that the endpoint he used for Celebrex previously had not been used in a published COX-2 meta-analyses[8]
How was the cause of death determined?	Cause of death determined by the patient's physician or by an independent committee[9]	Cause of death determined by the patient's physician or by an independent committee[10]	Cause of death assigned by Plaintiffs' other experts with unknown criteria [11]	Admitted that assignment of cause of deaths was performed arbitrarily by other Plaintiffs' experts[12]
Were the endpoints clearly defined in advance?	Endpoints are always clearly defined in writing in advance[13]	Endpoints were always clearly defined in writing in advance[14]	No agreement on definition of endpoints[15]	Admitted that he did not know if physicians understood his definitions of endpoints[16]
Was adjudicated data used whenever available?	Yes[17]	Yes[18]	No. Ignored available adjudicated data.[19]	Admitted that he ignored available adjudicated data, even though he agreed that such adjudicated data was more reliable.[20]

Sources for Fig. 1

[1] Markel Decl., Ex. 60 at 1302-03 (Kearney et al., BRIT. MED. J., 2006;332(7553)); *see also* Markel Decl., Ex. 8 at 64 (Furberg Dep.).
[2] Markel Decl., Ex. 99 at 82-83 (Madigan Grutka Dep.).
[3] Markel Decl., Ex. 13 at 99-100, 253 (Madigan Dep.).
[4] Markel Decl., Ex. 13 at 99-100, 204, 253 (Madigan Dep.).
[5] Markel Decl., Ex. 13 at 255-57 (Madigan Dep.); *see also* Markel Decl., Ex. 60 at 1302-03 (Kearney et al., BRIT. MED. J., 2006;332(7553):1302-1308); Markel Decl., Ex. 55 at 4 (FDA Decision Mem. [analyzing APTC endpoint]).
[6] Markel Decl., Ex. 13 at 236, 259 (Madigan Dep.); Markel Decl., Ex. 100 at 2 (Madigan Vioxx Rep.).
[7] Markel Decl., Ex. 13 at 89, 229-31 (Madigan Dep.).
[8] Markel Decl., Ex. 13 at 255-57 (Madigan Dep.).
[9] Markel Decl., Ex. 60 at 1305 (Kearney et al., BRIT. MED. J., 2006;332(7553):1302-08).
[10] Markel Decl., Ex. 100 at 14 (Madigan Vioxx Rep.).
[11] Markel Decl., Ex. 161 at 20-22, 38-42, 77-80, 128, 131, 163-64 (Baruch Dep.); Markel Decl., Ex. 13 at 44-51, 65-66, 249-250 (Madigan Dep.).
[12] *Id.*
[13] *See, e.g.*, Markel Decl., Ex. 11 at 82 (Antiplatelet Trialist Collaboration, BRIT. MED. J., 1994;308:81-106).
[14] Markel Decl., Ex. 99 at 86 (Madigan Grutka Dep. [including in his analysis the events that "were included under Merck's definition of a thrombotic event as provided to [him] by Drs. Cotsis and Krumholz"]).
[15] Markel Decl., Ex. 161 at 20-22, 38-44, 46-48, 163-64 (Baruch Dep.); Markel Decl., Ex. 13 at 247 (Madigan Dep.).
[16] Markel Decl., Ex. 13 at 246 (Madigan Dep.).
[17] *See, e.g.*, Markel Decl., Ex. 11 at 82-83 (Antiplatelet Trialist Collaboration, BRIT. MED. J. 1994;308:81-106).
[18] *See* Markel Decl., Ex. 13 at 242-43 (Madigan Dep.).
[19] Markel Decl., Ex. 13 at 60, 63-64, 100-01, 253 (Madigan Dep.).
[20] Markel Decl., Ex. 13 at 60, 63-64, 100-01, 253 (Madigan Dep.).

FIGURE 2

The Impact of Furberg's Post Hoc, Undisclosed, Unwritten, Unblinded Reclassification of a Select Group of Events on Madigan's Results

Dose	Classification	Hard CHD	Myocardial Thromboembolic Events	Cardiovascular Thromboembolic Events	Cardiovascular Mortality
All doses	Baruch Classification	P=0.2	P=0.09	P=0.3	----
	Furberg Reclassification	P=0.2	P=0.07	P=0.6	P=0.2
400 mg or greater	Baruch Classification	P=0.1	P=0.05	----	----
	Furberg Reclassification	P=0.04	P=0.02	P=0.3	P=0.1

FIGURE 3

Furberg's Unfounded Drug Safety Positions

Drug (Manufacturer)	Furberg's Claim	Furberg's Methods Criticized by Peers	Concerns Accepted by FDA Leading to Change in Label	Concerns Currently Described in Medical Textbooks	Results of Subsequent Studies
Gemfibrozil for lipid lowering (Pfizer)	Drug *increased* risk of death[1]	----	No	No	Drug *reduced* major cardiovascular ("CV") events[2]
Nifedipine in coronary heart disease (Pfizer)	Drug *increased* risk of death[3]	Yes[4-6]	No	No	Drug did *not* increase risk of death; it *reduced* need for cardiac procedures[7]
Nifedipine, amlodipine and other calcium channel blockers (Pfizer)	Drugs *increased* risk of gastrointestinal ("GI") bleeding	Yes[13]	No	No	Drugs had *less* risk of GI bleeding than other drugs and did not increase risk of cancer or dementia[11]
	Drugs *increased* risk of various cancers[9,10]		No	No	
	Drugs *increased* risk of dementia[12]		No	No	Drugs *reduced* risk of dementia[14]
Nifedipine, amlodipine and other calcium channel blockers in hypertension (Pfizer)	Drugs *increased* risk of myocardial infarction[15]	Yes[16-18]	No	No	Drugs *reduced* the risk of serious CV event more than other drugs[19]
Tiotropium in chronic lung disease (Pfizer)	Drug *increased* risk of cardiovascular death, myocardial infarction and stroke[20]	----	No;[21] initial concern withdrawn	No	Drug *reduced* the risk of death and did not increase CV risk[22]
Rosiglitazone for diabetes (GlaxoSmith Kline)	Drug *increased* long-term risk of myocardial infarction[23]	----	Long-term risk not cited and deemed inconclusive[24]	No	No confirmation in large-scale trial; similar drug *decreased* risk of CV events[25-27]

Sources for Fig. 3

[1] Gould et al., CIRCULATION 1995;91:2274-82 (Markel Decl., Ex. 135).
[2] Rubins et al., N ENGL J MED 1999;341:410-8 (Markel Decl., Ex. 136).
[3] Furberg et al., CIRCULATION 1995;92:1326-31 (Markel Decl., Ex. 137).
[4] Opie & Messerli, CIRCULATION 1995;92:1068-73 (Markel Decl., Ex. 138).
[5] Kloner, CIRCULATION 1995;92:1074-8 (Markel Decl., Ex. 139).
[6] Rafflenbeul et al., EUR HEART J 1996;17:1147-52 (Markel Decl., Ex. 140).
[7] Poole-Wilson et al., LANCET 2004;364:849-57 (Markel Decl., Ex. 141).
[8] Pahor et al., LANCET 1996;347:1061-65 (Markel Decl., Ex. 142).
[9] Fitzpatrick et al., CANCER 1997;80:1438-47 (Markel Decl., Ex. 143).
[10] Pahor & Furberg, DRUGS AGING 1998;13:99-108 (Markel Decl., Ex. 144).
[11] Leenen et al., HYPERTENSION 2006;48:374-84 (Markel Decl., Ex. 145).
[12] Heckbert et al., J. AM. GERIATR. SOC. 1997;45:1423-33 (Markel Decl., Ex. 146).
[13] Steven Milloy, *Junk Science: Diabetes Drug Scare or Scam?* FOXNews.com, June 10, 2007, available at http://www.foxnews.com/story/0,2933,279079,00.html (last visited July 8, 2009) (Markel Decl., Ex. 147).
[14] Forette et al., ARCH INTERN MED 2002;162:2046-52 (Markel Decl., Ex. 148).
[15] Pahor et al., LANCET 2000;356:1949-54 (Markel Decl., Ex. 149).
[16] Kaplan, LANCET 2000;356:1933 (Markel Decl., Ex. 150).
[17] Zosia Chustecka, *Experts Condemn Furberg's Meta-Analysis Showing Calcium Channel Blockers to be Inferior*, HEARTWIRE, Sept. 1, 2000 at 1-2 (quoting Dr. Stephen Nissen and Dr. Peter Server) (Markel Dec. Ex. 107)
[18] Middeke, DTSCH MED WOCHENSCHR. 2001;126:151-52 (Markel Decl., Ex. 151).
[19] ALLHAT Officers and Coordinators for the ALLHAT Collaborative Research Group, JAMA 2002;288:2981-97 (Markel Decl., Ex. 152).
[20] Singh et al., JAMA 2008;300:1439-50 (Markel Decl., Ex. 153).
[21] Smith, *FDA Eases Stroke Concerns for Tiotropium in COPD Therapy*, MedPage Today, Oct. 7, 2008 (Markel Decl., Ex. 154).
[22] Tashkin et al., N. ENGL. J. MED. 2008;359:1543-54 Epub 2008 Oct 5 (Markel Decl., Ex. 155).
[23] Singh et al., JAMA 2007;298:1189-95 (Markel Decl., Ex. 156).
[24] Avandia Label (Oct. 2008) (Markel Decl., Ex. 157)
[25] Home et al., LANCET 2009;373:2125-35 Epub 2009 Jun 6 (Markel Decl., Ex. 158).
[26] Home et al., N. ENGL. J. MED. 2007;357:28-38 Epub 2007 Jun 5 (Markel Decl., Ex. 159).
[27] Lincoff et al., JAMA 2007;298:1180-8 (Markel Decl., Ex. 160).

FIGURE 4

Totality of Endpoints in Celebrex Clinical Trials
Comparison of Celebrex to Placebo

	Primarily Thrombotic Events Alleged by Plaintiffs To Be Consistent With FitzGerald Hypothesis					Nonthrombotic Events or Mixture of Thrombotic and Nonthrombotic Events					
	Myocardial infarction	Fatal myocardial infarction	Fatal and nonfatal myocardial infarction + sudden death	Cardiovascular death	CV death + myocardial infarction + stroke (APTC)	Heart failure	CV death + myocardial infarction + stroke + heart failure	Myocardial thromboembolic adverse events	Cardiovascular thromboembolic adverse events	All-cause mortality	General cardiovascular disorders: heart rate and rhythm disorders; myocardial, endocardial, pericardial and valve disorders
Trials of Celebrex (≥ 200 mg Daily) vs Placebo Completed Before December 2004											
221-ALS											
635-IFL-0508-003											
635-IFL-0508-010											
A3191051											
A3191052											
A3191053											
A3191062											
A3191063											
A3191069											
A3191071											
A3191082											
COXA-0508-146											
COXA-0508-244											
COXA-0508-245											
COXA-0508-249											
COXA-0508-253											
COXA-0508-269											
COXXNT-6570-001											
F49-98-02-137											
IQ5-97-02-001											✓
EQ5-98-02-002											
J49-01-02-216											
N49-01-02-193											
N49-01-02-198											
N49-01-02-200											
N49-01-02-201											
N49-96-02-012											
N49-96-02-013											
N49-96-02-020											
N49-96-02-021											
N49-96-02-022											
N49-96-02-023											
N49-96-02-047											
N49-96-02-054											
N49-96-02-060											
N49-98-02-087											
N49-98-02-118											
N49-99-02-152											
NQ4-00-02-011											
NQ4-99-02-008											
NQ5-98-02-005											
Trials of Celebrex (≥ 200 mg Daily) vs Placebo Completed During or After December 2004											
NQ8-00-02-004											
A3191174											
20010836											
COXAON-0509-125											
ADAPT											
APC							✓				
PreSAP											

☐ Not identified by Plaintiffs as statistically significant

✓ Identified by Plaintiffs as statistically significant

There were 451 possible analyses of the endpoints proposed by the Plaintiffs in the 41 placebo-controlled trials with Celebrex that were carried out before December 2004. Only one of the 451 analyses was statistically significant, and this was for an endpoint that had no relation to the risk of thrombotic cardiovascular events.

FIGURE 5

Totality of Endpoints in Celebrex Clinical Trials
Comparison of Celebrex to Non-selective NSAIDs

	Primarily Thrombotic Events Alleged by Plaintiffs To Be Consistent With FitzGerald Hypothesis					Nonthrombotic Events or Mixture of Thrombotic and Nonthrombotic Events					
	Myocardial infarction	Fatal myocardial infarction	Fatal and nonfatal myocardial infarction + sudden death	Cardiovascular death	CV death + myocardial infarction + stroke (APTC)	Heart failure	CV death + myocardial infarction + stroke + heart failure	Myocardial thromboembolic adverse events	Cardiovascular thromboembolic adverse events	All-cause mortality	General cardiovascular disorders; heart rate and rhythm disorders; myocardial, endocardial, pericardial and valve disorders
Trials of Celebrex (≥ 200 mg Daily) vs Nonselective COX-2 Inhibitors Completed Before December 2004											
I49-96-02-042											
N49-96-02-020											
N49-96-02-023											
I49-96-02-041											
N49-96-02-021											
N49-96-02-054											
N49-97-02-062											
N49-97-02-071											
N49-96-02-022											
F49-98-02-137											
N49-98-02-118											
I49-98-02-106											
F49-98-02-122											
CLASS											
SUCCESS											
I49-98-02-105											
I49-98-02-107											
A3191025											
A3191006											
J49-01-02-217											
N49-01-02-201											
J49-01-02-216											
635-IFL-0508-002											
A3191051											
A3191053											
N49-01-02-193											
A3191063											
COXA-0508-253											
A3191052											
A3191062											
A3191071											
COXA-0508-247											
Trials of Celebrex (≥ 200 mg Daily) vs Nonselective COX-2 Inhibitors Completed During or After December 2004											
ADAPT											
A3191152											
COXA-0508-243											
A3191174											

☐ Not identified by Plaintiffs as statistically significant
✓ Identified by Plaintiffs as statistically significant

There were 352 possible analyses of the endpoints proposed by the Plaintiffs in the 32 NSAID-controlled trials with Celebrex that were carried out before December 2004. Only one of the 352 analyses was statistically significant (SUCCESS), and it showed that Celebrex significantly *reduced* the risk of heart failure compared to non-selective NSAIDs, which Plaintiffs' experts ignored.

FIGURE 6

Totality of Endpoints in Bextra and Parecoxib Clinical Trials

Comparison of Bextra and/or Parecoxib to Placebo, NSAIDs or Standard of Care

	Primarily Thrombotic Events Alleged by Plaintiffs To Be Consistent With FitzGerald Hypothesis						Nonthrombotic Events or Mixture of Thrombotic and Nonthrombotic Events					
	Myocardial infarction	Fatal myocardial infarction	Fatal and nonfatal myocardial infarction + sudden death	Cardiovascular death	CV death + myocardial infarction + stroke (APTC)	CV death + myocardial infarction or ischemia + stroke or transient ischemic attack + deep vein thrombosis + pulmonary embolism	Heart failure	CV death + myocardial infarction + stroke + heart failure	Myocardial thromboembolic adverse events	Cardiovascular thromboembolic adverse events	All-cause mortality	General cardiovascular disorders: heart rate and rhythm disorders; myocardial, endocardial, pericardial and valve disorders
Trials of Bextra vs Placebo Completed Before December 2004												
N91-97-02-015												
N91-97-02-016												
N91-98-02-048												
N91-99-02-049												
N91-99-02-053												
N91-99-02-060												
N91-99-02-061												
872-IFL-0513-004												
VALA-0513-142												
VALA-0513-143												
N91-01-02-097												
N91-01-02-108												
N91-01-02-132												
N91-01-12-133												
N91-01-32-040											✓	
Trials of Bextra vs Nonselective COX-2 Inhibitors Completed Before December 2004												
N91-97-02-015												
N91-97-02-016												
N91-99-02-047												
N91-98-02-048												
N91-99-02-049												
N91-99-02-053												
N91-99-02-060												
N91-99-02-061												
I91-99-02-062												
I91-99-02-063												
N91-00-02-079												
Trials of Intravenous Parecoxib Followed by Oral Bextra Completed Before December 2004												
93-035 (CABG-1)												
93-069 (Non-cardiac surgery)												
93-071 (CABG-2)												
IV Parecoxib + Bextra pills						✓						
Bextra pills only												
IV Parecoxib + Bextra pills combined with Bextra pills only												

☐ Not identified by Plaintiffs as statistically significant

✓ Identified by Plaintiffs as statistically significant

There were 312 possible analyses of the endpoints proposed by the Plaintiffs in the 26 Bextra pill trials that were carried out before December 2004. Only one of the 312 analyses was statistically significant, and that endpoint had no relation to the risk of thrombotic events. When adding the three experimental trials where patients took high doses of IV parecoxib followed by Bextra pills, of the 348 possible analyses of the endpoints in those 29 trials, only one additional analysis was statistically significant, and it was only in patients taking IV parecoxib followed by Bextra pills. Patients taking Bextra pills only - even when combined with the IV parecoxib group - were not at an increased risk of thrombotic events.